UDC 615.9; 615.322

Larysa BONDARENKO
Doctor of Biological Sciences, Principal Research Scientist of the Department of Toxicology, State Institution «Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine», Anton Tsedik str., 14, Kyiv, Ukraine, 03057
***ORCID:** 0000-0001-5107-8148*
***SCOPUS:** 7005441142*

Iryna BLAZHCHUK
Candidate of Biological Sciences, Senior Research Scientist of the Department of Toxicology, State Institution «Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine», Anton Tsedik str., 14, Kyiv, Ukraine, 03057
***ORCID:** 0009-0004-1962-1488*
***SCOPUS:** 6506623179*

Tetyana KARATSUBA
Candidate of Biological Sciences, Head of the Oncopharmacology Laboratory, State Institution «Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine», Anton Tsedik str., 14, Kyiv, Ukraine, 03057
***ORCID:** 0000-0003-4913-5953*
***SCOPUS:** 57096062000*

Sergey TISHKIN
Doctor of Biological Sciences, Principal Research Scientist of the Department of Pharmacology of Cell Signaling Systems and Experimental Therapy, State Institution «Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine», Anton Tsedik str., 14, Kyiv, Ukraine, 03057
***ORCID:** 0000-0001-5679-1743*
***SCOPUS:** 6603752444*

Maria KALACHINSKAYA
Specialist of the Biomedical Engineering Faculty, National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Beresteiskyi ave., 37, Kyiv, Ukraine, 03056
***ORCID:** 0000-0002-6940-2249*
***SCOPUS:** 58360797700*

Natalia SERHIICHUK
Senior Lecturer of the Department of Microbiology, Modern Biotechnologies, Ecology and Immunology, Open International University of Human Development «Ukraine», Lvivska str., 23, Kyiv, Ukraine, 03115
***ORCID:** 0000-0001-6690-0114*
***SCOPUS:** 58362673000*

Valentyna KOVALENKO
Doctor of Biological Sciences, Head of the Department of Toxicology, State Institution «Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine», Anton Tsedik str., 14, Kyiv, Ukraine, 03057
***ORCID:** 0000-0001-5782-6733*
***SCOPUS:** 7201830539*

Kateryna SHEVCHUK
PhD Student of the Translational Medical Bioengineering Department, National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Beresteiskyi ave., 37, Kyiv, Ukraine, 03056 (tmb@lll.kpi.ua)
***ORCID:** 0000-0001-9261-2255*

Oleksandr BESARAB
Candidate of Technical Sciences, Head of the Translational Medical Bioengineering Department, National Technical University of Ukraine «Igor Sikorsky Kyiv Polytechnic Institute», Beresteiskyi ave., 37, Kyiv, Ukraine, 03056 (besarab@lll.kpi.ua)
***ORCID:** 0000-0002-2087-6953*
***SCOPUS:** 56338279200*

To cite this article: Bondarenko L., Blazhchuk I., Karatsuba T., Tishkin S., Kalachinskaya M., Serhiichuk N., Kovalenko V., Shevchuk K., Besarab O. (2024). Klastohenni efekty ekstraktu *Veratrum album* L. u testi khromosomnykh aberatsii kistkovoho mozku shchuriv [Clastogenic effects of *Veratrum album* L. extract in a rat bone marrow chromosome aberration test]. *Fitoterapiia. Chasopys – Phytotherapy. Journal*, 3, 126–137, doi: https://doi.org/10.32782/2522-9680-2024-3-127

CLASTOGENIC EFFECTS OF *VERATRUM ALBUM* L. EXTRACT IN A RAT BONE MARROW CHROMOSOME ABERRATION TEST

Actuality. *Medicines containing various plants are becoming increasingly popular among the population of different countries all over the world. However, given the fact that many herbal preparations were included in the pharmacopeia long before the introduction of modern requirements for safety assessment and the development of new methods for such assessment, there is a risk of negative side effects when using such medicines. Veratrum album L. extract, dermal application in children could be accompanied by transcutaneous (by intense skin scratching) and per os – (by licking hands) entries into the organism. Adults may also ingest this substance by mistake. Using Veratrum album L. extracts as a pesticide against the Colorado potato beetle greatly increases the possibilities of its entry into the body.*

The aim of the research *was to investigate Veratrum album L. extract possible genotoxic effects in chromosomal aberration test.*

Material and methods. *Wistar albino rats were separated into five groups (10 animals in each group): 1 – negative control (intact rats), 2 – positive control (cyclophosphamide, 20 mg/kg b.w.), 3 – Veratrum album L. extract maximum tolerated dose (2.9 ml/kg b.w), 4 – Veratrum album L. extract ½ of maximum tolerated dose (1.45 ml/kg b.w), 5 – Veratrum album L. extract ¼ of maximum tolerated dose (0.73 ml/kg b.w). Both preparations (Veratrum album L. extract and cyclophosphamide) were administered intraperitoneally.*

Research results. *Veratrum album L. extract significantly changed percentage of aneuploid cells, mitotic index, chromatid and chromosomal aberrations. Gaps, fragments and breaks were the main types of chromatid aberrations, while the spectrum of chromosomal aberrations was much wider and these changes had dose dependent character.*

Conclusions. *Thus, in experiments in vivo, we have shown Veratrum album L. extracts clear dose-dependent clastogenic effect. The results obtained indicate the urgent need for additional assessment of herbal medicines' side effects and, first of all, those that are approved for use in children.*

Key words: *Veratrum album L. extract, chromosomal aberration test, clastogenic effect.*

Лариса БОНДАРЕНКО
доктор біологічних наук, головний науковий співробітник відділу токсикології, ДУ «Інститут фармакології і токсикології НАМН України», вул. Антона Цедіка, 14, м. Київ, Україна, 03057
ORCID: *0000-0001-5107-8148*
SCOPUS: *7005441142*

Ірина БЛАЖЧУК
кандидат біологічних наук, старший науковий співробітник відділу токсикології, ДУ «Інститут фармакології і токсикології НАМН України», вул. Антона Цедіка, 14, м. Київ, Україна, 03057
ORCID: *0009-0004-1962-1488*
SCOPUS: *6506623179*

Тетяна КАРАЦУБА
кандидат біологічних наук, завідувач лабораторією онкофармакології, ДУ «Інститут фармакології і токсикології НАМН України», вул. Антона Цедіка, 14, м. Київ, Україна, 03057
ORCID: *0000-0003-4913-5953*
SCOPUS: *57096062000*

Сергій ТИШКІН
доктор біологічних наук, головний науковий співробітник відділу фармакології клітинних сигнальних систем та експериментальної терапії, ДУ «Інститут фармакології і токсикології НАМН України», вул. Антона Цедіка, 14, м. Київ, Україна, 03057
ORCID: *0000-0001-5679-1743*
SCOPUS: *6603752444*

Марія КАЛАЧІНСЬКА
фахівець факультету біомедичної інженерії, Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського», просп. Берестейський, 37, м. Київ, Україна, 03056
ORCID: *0000-0002-6940-2249*
SCOPUS: *58360797700*

Наталія СЕРГІЙЧУК
старший викладач кафедри мікробіології, сучасних біотехнологій, екології та імунології, Відкритий міжнародний університет розвитку людини «Україна», вул. Львівська, 23, м. Київ, Україна, 03115
ORCID: *0000-0001-6690-0114*
SCOPUS: *58362673000*

Валентина КОВАЛЕНКО
доктор біологічних наук, завідувач відділу токсикології, ДУ «Інститут фармакології і токсикології НАМН України», вул. Антона Цедіка, 14, м. Київ, Україна, 03057
ORCID: *0000-0001-5782-6733*
SCOPUS: *7201830539*

Катерина ШЕВЧУК
аспірантка кафедри трансляційної медичної біоінженерії, Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського», просп. Берестейський, 37, м. Київ, Україна, 03056 (tmb@lll.kpi.ua)
ORCID: *0000-0001-9261-2255*

Олександр БЕСАРАБ
кандидат технічних наук, завідувач кафедри трансляційної медичної біоінженерії, Національний технічний університет України «Київський політехнічний інститут імені Ігоря Сікорського», просп. Берестейський, 37, м. Київ, Україна, 03056 (besarab@lll.kpi.ua)
ORCID: *0000-0002-2087-6953*
SCOPUS: *56338279200*

Бібліографічний опис статті: Бондаренко Л., Блажчук І., Карацуба Т., Тішкін С., Калачінська М., Сергійчук Н., Коваленко В., Шевчук К., Бесараб О. (2024). Кластогенні ефекти екстракту *Veratrum album* L. у тесті хромосомних аберацій на клітинах кісткового мозку щурів. *Фітотерапія. Часопис*. 3, 126–137, doi: https://doi.org/10.32782/2522-9680-2024-3-127

КЛАСТОГЕННІ ЕФЕКТИ ЕКСТРАКТУ *VERATRUM ALBUM* L. У ТЕСТІ ХРОМОСОМНИХ АБЕРАЦІЙ НА КЛІТИНАХ КІСТКОВОГО МОЗКУ ЩУРІВ

Актуальність. *Лікарські засоби, які містять різні рослини, набувають усе більшої популярності серед населення різних країн світу. Але враховуючи той факт, що багато рослинних препаратів були включені до фармакопеї задовго до запровадження сучасних вимог до оцінки безпеки та розроблення нових методів такої оцінки, існує ризик негативних побічних ефектів під час застосування цих препаратів. Нашкірне застосування екстракту Veratrum album L. у дітей може супроводжуватися через шкірне (шляхом інтенсивного розчісування шкіри) та per os – (шляхом облизування рук) його потрапляння в організм. Дорослі також можуть помилково проковтнути цю речовину. Застосування екстракту Veratrum album L. як пестициду проти колорадського жука значно збільшує можливості його потрапляння в організм.*

Мета дослідження. *Дослідити можливі генотоксичні ефекти екстракту Veratrum album L. у тесті на хромосомні аберації.*

Матеріал і методи. *Щурів лінії Wistar розподілили на 5 груп (по 10 тварин у кожній групі): 1 – контроль (інтактні щури), 2 – позитивний контроль (циклофосфамід, 20 мг/кг маси тіла), 3 – екстракт Veratrum album L. максимально переносима доза (2,9 мл/кг маси тіла), 4 – екстракт Veratrum album L. ½ максимально переносимої дози (1,45 мл/кг маси тіла), 5 – екстракт Veratrum album L. ¼ максимально переносимої дози (0,73 мл/кг маси тіла). Обидва препарати (екстракт Veratrum album L. і циклофосфамід) вводили внутрішньо-очеревинно.*

Результати дослідження. *Екстракт Veratrum album L. значно змінив відсоток анеуплоїдних клітин, мітотичний індекс, хроматидні та хромосомні аберації. Основними типами хроматидних аберацій були втрати, фрагменти та розриви, тоді як спектр хромосомних аберацій був значно ширшим, і ці зміни мали дозозалежний характер.*

Висновок. *Таким чином, в експериментах in vivo ми показали, що Veratrum album L. виявляє чіткий дозозалежний кластогенний ефект. Отримані результати свідчать про нагальну необхідність додаткової оцінки побічної дії фітопрепаратів, насамперед тих, які дозволені до застосування дітям.*

Ключові слова: *екстракт Veratrum album L., тест на хромосомні аберації, кластогенна дія.*

Introduction. Actuality. The use of plants as medicines by humans began in prehistoric times and this practice is successfully continued to this day in both developing and highly developed countries. Moreover, now medicines containing various plants are becoming increasingly popular among the population of different countries all over the world. In the minds of the current technogenic society, the stereotype about the safety and

usefulness of everything that is of natural origin, and herbal medicines, is no exception (Kislyak et al., 2024; Kurdil et al., 2024; Shevchenko et al., 2022).

However, given the fact that many herbal preparations were included in the pharmacopeia long before the introduction of modern requirements for safety assessment and the development of new methods for such assessment, there is a risk of negative side effects when using such medicines. Adopted in 2004 toughened international Directives on traditional herbal medicinal products for human use (Directive 2004/24/EC) did not completely solve the problem of our insufficient knowledge of such preparation's safety.

In the past centuries there were no methods for properly assessing the possible negative effects of drugs, or even an understanding of the need for these studies therefore, a preparation used for centuries without visible immediate negative consequences may well pose a serious health hazard. Quality of raw materials, method of preparation and chemical composition of the selected herbal substance, choice of doses, method and duration of use. dosage regimen, age of patients, interaction with other herbal or synthetic drugs – this is an incomplete list of reasons for the manifestation of negative effects in herbal medicines, as evidenced by the growing number of scientific publications (Krepkova et al., 2013).

More and more specialists are realizing that even a long and ostensibly successful history of herbal medicines use does not guarantee their safety, therefore, in some cases, the EU and USA regulatory authorities have the right to request additional data to evaluate the safety of any drug. Effective and safe phytopharmacotherapy needs to have full information not only about the pharmacologic activity of the herbal drug but also about its toxic influences on organs and tissues. That's why the need for more in-depth studies of herbal medicines safety is so relevant (Krepkova et al., 2013, Anywar et al., 2021).

In addition, the toxicity of some drugs traditionally was considered acceptable due to the absence of their systemic action. However, in practice such an action often occurs. The inappropriate use of drugs also can be a source of danger.

An example of such medicine would be a common antiparasitic agent – Veratri Aqua (*Veratrum album L.* extract). There are extremely contradictory data in the scientific literature regarding the safety of herbal preparations from various species of the *Veratrum genus* (Christov et al., 2010; Vachálková et al., 1998). As for Veratri Aqua, it must be noted, that a significant portion of total patients' population, for whom it is used, is represented by toddlers and children. *Veratrum album L.* extract, dermal application in children could be accompanied by transcutaneous (by intense skin scratching) and *per os* – (by licking hands) entries into the organism.

Adults may also ingest this substance by mistake. There are some reports on acute dietary poisoning by *Veratrum album L.* (Garnier et al., 1985; Grobosch et al., 2008). These cases of acute accidental poisoning occurred due to the use of home-made gentian wine. *Veratrum album L.* and *Gentiana lutea L.* often grow next to each other in the fields, where it is easy to confuse the two plants if one is not a botanist.

Using *Veratrum album L.* extracts as a pesticide against the Colorado potato beetle greatly increases the possibilities of its entry into the body (Aydin et al, 2014).

The prevailing conditions pose a potential danger of not just local but systemic harmful effects of the *Veratrum album L.* extracts on the organism.

The aim of the study was to investigate *Veratrum album L.* extract possible genotoxic effects in chromosomal aberration test.

Materials and methods. 1 ml of the Veratri Aqua contains tincture (1:10) of hellebore rhizomes with roots (veratri rhizomata cum radicibus) – 0.5 ml; extractant: ethanol 70% (v/v), purified water. Veratri Aqua was purchased by "Khimpharmzavod Chervona Zirka", Ukraine (UA/9250/01/01), cyclophosphamide monohydrate – by Baxter Oncology Co., Germany (Ser.41033C), colchicine – by Sigma-Aldrich International GMBH, Switzerland (Lot#SLBL0409V), Giemsa stain – by Sigma-Aldrich International GMBH, Switzerland (Lot#SLBH0211V).

A total of 50 Wistar albino female rats (160–180g) were used in the study. Conditions for keeping experimental animals: controlled temperature (22-24 °C), humidity (relative) – 40–70 %, lighting – 12 h light-dark cycle, feed – standard diet ("Phoenix" Ltd., Ukraine). All experimental procedures were carried out accordingly with the recommendations of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (Galkin et al., 2013). They were approved by the Institutional Animal Care and Use Committee. The experimental design included the presence of five groups (10 animals in each group): 1 – negative control (intact rats), 2 – positive control (cyclophosphamide, 20 mg/kg b.w.), 3 – Veratri Aqua maximum tolerated dose (2.9 ml/kg b.w), 4 – Veratri Aqua ½ of maximum tolerated dose (1.45 ml/kg b.w), 5 – Veratri Aqua ¼ of maximum tolerated dose (0.73 ml/kg b.w). Taking into account the uncontrollable widespread use of the Veratri Aqua for children (including toddlers) pediculosis treatment, these doses are quite consistent with possible human real-life exposures.

Veratrum album L. extract and cyclophosphamide were administered by intraperitoneal injection (one single dose) 24 hours before euthanization. Animals were weighed before administration of substances to ensure that the weight of each animal was within 20% of the mean weight (recommended by the guideline (Grobosch et al., 2008)). Clinical signs of toxicity were determined in all experimental animals at specified times after substances administration. A metaphase arresting agent colchicine (2.5 mg/kg) was administered intraperitoneally to animals two hours before scheduled euthanization.

Bone marrow chromosome aberration test (OECD Guideline for the Testing of Chemicals, 1997). After animals' euthanization, we removed femurs, cut off the epiphyses and flushed the bone marrow out with a 0.075M KCl solution. Collected cells were incubated (37°C for 40 min). Cell suspensions were then spun in a centrifuge (1000 g for 5 min). The supernatant was discarded. The bone marrow cells in the pellet were resuspended in 6 ml of ice-cold fixing solution (3:1 ethanol: glacial acetic acid) under vigorous mixing. The mixture was left in freezing camera for 40 min and then bone marrow cells were sedimented by centrifugation (1000 g for 5 min). The supernatant was discarded (Guide to short-term tests for identify mutagenic and carcinogenic chemicals, 1989, Holstein, 1973).

For preparation of microscopic slides, we dropped 3–4 drops of cells' suspension on clean ice-cold slides, flame-dried them, and then stained with Giemsa dye during 5 min. After these finished slides were blindly marked and examined under a microscope using 100X oil immersion objectives. Cytogenetic damage (chromosome breaks, fragments, deletions, exchanges and disintegrations) for each animal was scored on 100 (at least) well-spread metaphases (Holstein, 1973). Gaps and polyploidy were recorded. Determination of the degree of cytotoxicity on bone marrow cells was carried out by analyzing at least 100 cells for each animal for the percentage of cells in mitosis (mitotic index).

We present the experimental data as mean ± standard error. For statistical analysis of the obtained results, we used the software STATISTICA 10 (StatSoft Inc., USA). First, we checked the normality and homogeneity of the distribution of the obtained data using the Shapiro-Wilk and Levene tests (respectively) and then applied parametric or non-parametric tests to analyze the difference between treatments (Galkin et al., 2017; Grigorieva et al., 2019). We performed univariate analysis of variance (ANOVA) for normal data distribution (aneuploidy and mitotic index) followed by Tukey's a posteriori analysis. When statistical processing of data on chromatid and chromosomal aberrations (non-parametric distribution) Kruskel-Wallis analysis or Mann-Whitney criterion (respectively) were used. Differences were considered statistically significant at $P<0.05$.

Research results. The results of the study are presented in Table 1 and Figures 1–14. By chromosomal aberration test in bone marrow cells of white rats the diploid set of intact *Rattus norvegicus* chromosomes was identified: 2n = 42 (fig. 1).

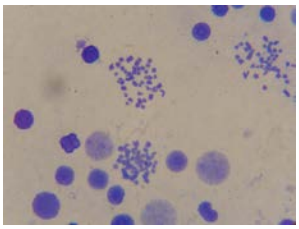

Fig. 1. The diploid set of *Rattus norvegicus* chromosomes in norm. Gimsa dye, × 1000

Control animals did not have chromosomal aberrations and polyploid cells. Regarding the spontaneous aberrations of the chromatide type, they were represented only by gaps and breaks, and their frequency did not exceed 1.8%, which is within the limits of the physiological norm (Guide to short-term tests for identify mutagenic and carcinogenic chemicals, 1989; Holstein, 1973).

Results of mutagenicity investigation of cyclophosphamide (positive control) in the chromosomal aberration test are shown in fig. 2 and fig. 3, as well as in table.

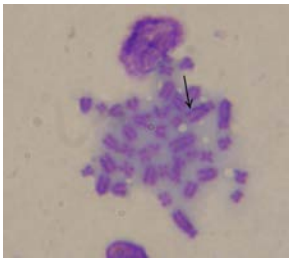

Fig. 2. Chromosomal aberration (break) in the diploid set of *Rattus norvegicus* chromosomes with administration of cyclophosphamide at a dose of 40 mg/kg (positive control). Gimsa dye, × 1000

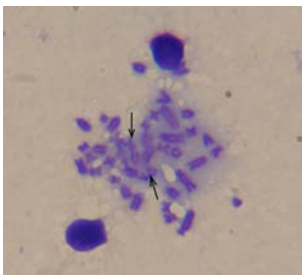

Fig. 3. Chromosomal aberrations (associations) in the diploid set of *Rattus norvegicus* chromosomes with administration of cyclophosphamide at a dose of 40 mg/kg (positive control). Gimsa dye, × 1000

In animals with cyclophosphamide, the total frequency of aberrant cells increased near 8-fold, which is due to the known mutagenic action of cyclophosphamide and this fact is evidence of adequate experimental conditions (Guide to short-term tests for identify mutagenic and carcinogenic chemicals, 1989). In this case, aberrations of the chromosomal type predominated. Their frequency was 8 times higher than chromatide aberrations. Gaps, fragments, breaks, rings and chromosomal associations were marked. Polyploid cells had not been detected. The percentage of aneuploid cells increased from 3.10% in control group up to 12.30% with cyclophosphamide with simultaneous decreasing of mitotic index from 4.91% up to 1.88%.

The data obtained clearly demonstrate that Veratri Aqua has a significant impact on most of the parameters studied when compared to the control group. Specifically, administration of all doses of Veratri Aqua led to a notable increase in the percentage of aneuploid cells, ranging from 5.10% with a dosage of 0.73 ml/kg to 6.70% with a dosage of 2.90 ml/kg. Additionally, the mitotic index decreased in a dose-dependent manner with Veratri Aqua treatment, dropping from 2.40% to 1.48%. The highest dosage of Veratri Aqua resulted in a statistically significant decrease in this parameter, not only compared to the control group but also when compared to the cyclophosphamide group.

Gaps, fragments and breaks were the main types of chromatid aberrations, while the spectrum of chromosomal aberrations was much wider and these changes had dose dependent character.

With Veratri Aqua administration in the minimal dose total number of aberrant metaphases increased in comparison with control 9.1 times (tabl. 1, fig. 4–8).

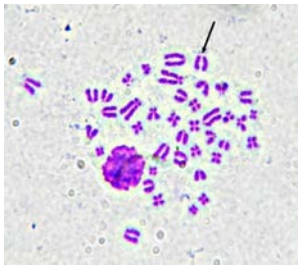

Fig. 4. Chromosomal aberrations (breaks) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 0.73 ml/kg b.w. (minimal dose). Gimsa dye, × 1000

Table 1

Results of cytogenetic analysis of rat bone marrow cells after Veratri Aqua administration

Index	Control	Cyclophosphamide, 20 mg/kg	Veratri Aqua, 0.73 ml/kg	Veratri Aqua, 1.45 ml/kg	Veratri Aqua, 2.90 ml/kg
Total number of cells in the metaphase	1000	1000	1000	1000	1000
Percentage of polyploid cells (%)	0	0	0	0	0
Aneuploidy (%)	3.10±0.31	12.30±0.50*	5.10±0.28*	5.80±0.20*	6.70±0.15*, **, ***
Mitotic index	4.91±0.14	1.88±0.03*	2.40±0.10*	2.04±0.11*	1.48±0.10*, **, ***
Number of structural violations per 100 metaphases					
Chromatide aberrations:	1.80±0.25	2.70±0.52	1.00±0.45	0.60±0.27*	0
-gaps, %	1.40±0.27	1.30±0.26	0.30±0.15*	0.40±0.22*	0
-fragments, %	0	0.30±0.21*	0.30±0.15*	0.10±0.10*	0
-breaks, %	0.40±0.16	1.10±0.35	0.40±0.22	0.10±0.10	0
Chromosome aberrations:	0	11.1±0.73*	15.40±0.34*	19.50±0.73*,#	26.00±0.80*,#, ##
– gaps, %	0	1.70±0.33*	2.70±0.26*	4.20±0.29*,#	5.50±0.22*,#, ##
– fragments, %	0	2.50±0.31*	3.30±0.26*	4.20±0.20*,#	6.10±0.28*,#, ##
-breaks, %	0	2.40±0.31*	4.50±0.22*	4.70±0.26*	5.90±0.23*,#, ##
-rings, %	0	0.90±0.18*	1.90±0.18*	1.80±0.20*	3.40±0.22*,#, ##
– dicentric chromosomes, %	0	0	0	0	0.30±0.15*
-fragmentation, %	0	0	0	0.20±0.13*	0
-chromosome associations, %	0	3.20±0.25*	2.70±0.40*	4.10±0.23*,#, ##	4.70±0.15*,#, ##
-deletions, %	0	0.40±0.16*	0.30±0.15*	0.30±0.15*	0.50±0.17*,
Total number of aberrant metaphases, %	1.80±0.25	13.90±1.17*	16.40±0.37*	20.70±0.45*, #	26.00±0.80*, #, ##

* – P<0,05 compared with control group;

**– P<0,05 compared with 0,73 ml/kg treatment by parametric tests;

#– P<0,05 compared with 0,73 ml/kg treatment by nonparametric tests;

***– P<0,05 compared with 1,45 ml/kg treatment by parametric tests;

– P<0,05 compared with 1,45 ml/kg treatment by nonparametric tests

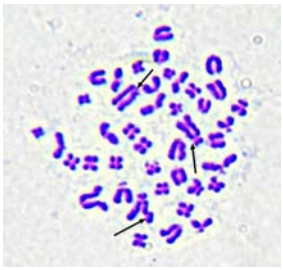

Fig. 5. Chromosomal aberrations (gaps, breaks, associations) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 0.73 ml/kg b.w. (minimal dose). Gimsa dye, × 1000

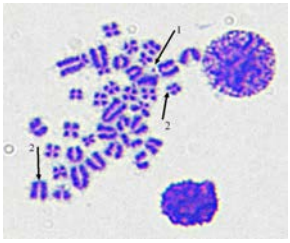

Fig. 6. Chromosomal aberrations (fragment (1), breaks (2)) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 0.73 ml/kg b.w. (minimal dose). Gimsa dye, × 1000

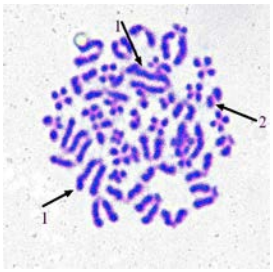

Fig. 7. Chromosomal aberrations (associatations (1), breaks (2)) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 0.73 ml/kg b.w. (minimal dose). Gimsa dye, × 1000

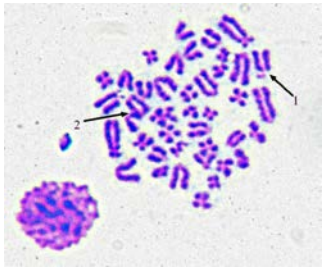

Fig. 8. Chromosomal aberrations (break (1), association (2)) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 0.73 ml/kg b.w. (minimal dose). Gimsa dye, × 1000

These aberrations were represented both by chromatide (1%) and chromosomal (15.40%) ones. Most of the changes were chromosomal breaks (4.50%) and chromosomal fragments (3.30%).

The administration of Veratri Aqua at a medium dose resulted in a reduction in the number of chromatide aberrations, while simultaneously increasing the number of chromosomal aberrations and total aberrant metaphases (table, fig. 9–11).

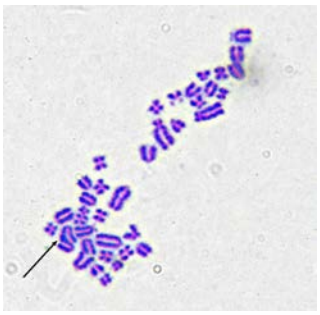

Fig. 9. Chromosomal aberration (association) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 1.45 ml/kg b.w. (medium dose). Gimsa dye, × 1000

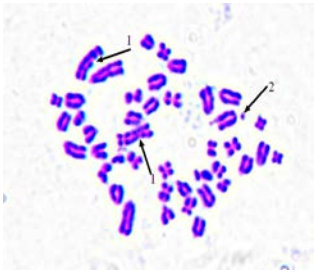

Fig. 10. Chromosomal aberrations (break (1), fragment (2)) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 1.45 ml/kg b.w. (medium dose). Gimsa dye, × 1000

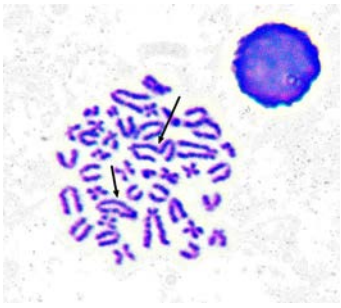

Fig. 11. Chromosomal aberrations (associations) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 1.45 ml/kg b.w. (medium dose). Gimsa dye, × 1000

At this dosage level, gaps, fragments, chromosome breaks, and their associations were predominant, while the percentage of rings remained consistent with that observed with the minimal dose of Veratri Aqua.

And finally, Veratri Aqua maximum dose expectedly led to the highest number of total aberrant metaphases (14.4 times higher the intact control level) with simultaneous total absence of chromatide aberrations (table, fig. 12–14).

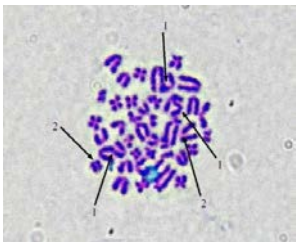

Fig. 12. Chromosomal aberrations (associations (1), breaks (2)) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 2.90 ml/kg b.w. (maximal dose). Gimsa dye, × 1000

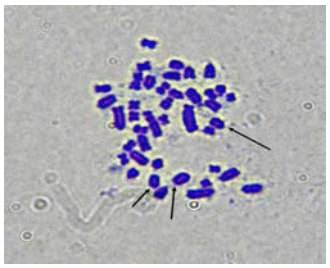

Fig. 13. Chromosomal aberrations (ring chromosomes (end locus deficiency)) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 2.90 ml/kg b.w. (maximal dose). Gimsa dye, × 1000

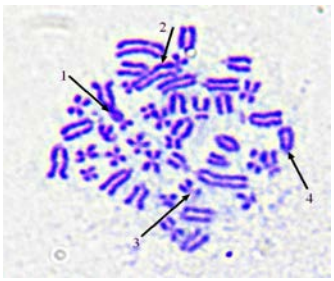

Fig. 14. Chromosomal aberrations (dicentric chromosome (1), chromatide break (3), association (2), ring chromosome (4)) in the diploid set of *Rattus norvegicus* chromosomes with administration of Veratri Aqua at a dose of 2.90 ml/kg b.w. (maximal dose). Gimsa dye, × 1000

At this dose, fragments and breaks accounted for the largest percentage of chromosomal aberrations. The percentage of rings was doubled compared with smaller doses.

Discussion. The situation with the widespread and often uncontrolled use of herbal medicines by the population (especially for children) remains serious not only in developing countries but also in Europe (Grosu et al., 2020; Klochko et al., 2023). This is largely due to historical traditions, the fact that people consider such medicines to be "safer" than products of chemical synthesis, "natural", whose safety has been tested in practice for hundreds of years. The situation is aggravated by the fact that even if there is data on a modern assessment of the safety of certain herbal preparations in adults, for the pediatric population such information is almost completely absent, although herbal preparations are most often used in children.

Even at the regulatory level, the situation with the assessment of the safety of herbal preparations is changing extremely slowly. In addition to the previously mentioned "Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use" (Directive 2004/24/EC) only one document regarding safety issues of herbal medicines has been prepared and approved in 2011 – "Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the paediatric population" (European Medicines Agency, 2012). And it remains current.

At the same time, there is a constant accumulation of scientific data on various manifestations of toxicity of long-used herbal preparations and their components. In particular, for plants from the Veratrum genus, the presence of toxic effects on the gastrointestinal tract, cardiovascular system, hormonal status, as well as teratogenicity was confirmed (Seale et al., 2022).

According to most researchers, such negative effects are due to the biological activity of alkaloids cyclopamine, veratramine, jervine, and muldamine whose presence has been confirmed in Veratrum spp. (Veratrum nigrum L., Veratrum californicum, Veratrum album L., Veratrum viride) (Seale et al., 2022).

Our results are in full agreement with the above-mentioned data of other researchers. Veratri Aqua even at a minimal dose demonstrates profound clastogenic effect as our data clearly demonstrates. The processes of cell division change significantly when *Veratrum album* L. extract is introduced into the body, and first of all, this results in a rise in the count of aneuploid cells and a proportional increase in chromosomal aberrations, accom-

panied by a corresponding decline in the mitotic index as the dosage increases. The observed changes may indicate a pronounced cytostatic effect of Veratri Aqua.

It should be noted, that Veratri Aqua clastogenic effect is realized simultaneously both by suppressing cell division processes and by disrupting the very structure of their chromosomes. The data we obtained regarding the dependence of the degree of increase in the percentage of chromosome fragments on the dose of the extract are quite consistent with this assumption.

Perhaps it is precisely through this mechanism that the teratogenic effect of plant alkaloids of the Veratrum genus noted by other researchers is realized (Krepkova et al., 2013; Christov et al., 2010; Vachálková et al., 1998; Garnier et al., 1985; Grobosch et al., 2008; Aydin et al., 2014; Seale et al., 2022).

In addition to the actual genotoxic effects of alkaloids in our experiments, one cannot ignore the genotoxicity of ethanol, as the main solvent of the extract *Veratrum album* L., the presence of which was shown by other authors *in vitro* in cytokinesis blocked micronucleus assay (Kayani et al, 2010).

Our data regarding the presence of a pronounced clastogenic effect in Veratri Aqua is in good accordance with another authors results on several alkaloids (from *Veratrum album L.*) impact on the inclusion of ^{3}H-thymidine into DNA within normal HepG2 cells (Gebhardt, 2003). Effects in HepG2 hepatoblastoma cells of homeopathic medicines serial dilutions (Carduus marianus from *Silybum marianum L.*, Nux moschata from *Myristica fragans,* Chelidonium from *Chelidonium majus L.*, Colocynthis from *Citrullus colocynthis L.*, Veratrum from *Veratrum album L.*, Lycopodium from *Lycopodium clavatum L.*, *Houtt*, and China from *Cinchona pubescens, Vahl*. tinctures) were examined, either individually or in different combinations. The statistically significant ($p < 0.01$) antiproliferative impact on normal HepG2 cells declined in the following order: Carduus marianus, Chelidonium, Colocynthis, and Veratrum (Gebhardt, 2003). The cytostatic effect observed with the combination of Colocynthis and Veratrum was notably greater (22.3%) compared to when the drugs were administered separately, although complete summation or synergism of effects was not observed (Gebhardt, 2003). The use of this combination causes a noticeable decrease in the number of cells. It should be noted that this combination equally affects the proliferation and number of cells starting from its dilutions of 1:40.

The potential tumor-inhibiting effects of six alkaloids isolated from different parts of *Veratrum album subsp. Lobelianum*, one from *Veratrum nigrum*, and three from *Peganum nigellastrum* were investigated in experiments conducted on multidrug-resistant human MDR1-gene-transfected mouse lymphoma cells (L5178Y) (Ivanova et al., 2003). This effect is apparently mediated by the influence of these compounds on MDR1 transport activity. The capability of alkaloids to impede multidrug resistance was assessed by quantifying the accumulation of rhodamine-123 in cancer cells. Veralosinine and veranigrine had proven to be the most effective resistance modifiers. In experiments using a checkerboard test combination of these compaunds enhanced the antiproliferative effects of doxorubicin on MDR cells. Experiments had revealed even some structure-activity relationships (Ivanova et al., 2003).

Furthermore, in addition to these effects, it is evident that Veratri Aqua steroidal alkaloids, similar to other compounds of this class, have the ability to trigger apoptosis and halt the cell cycle at the G2/M phase (Jin et al., 2018). The primary anticipated targets of steroidal alkaloids within cells were AKT and cyclin-dependent kinase 2 (CDK2). Another plant steroidal alkaloid, solanidine, triggers the intrinsic apoptotic signal through DFF-40 nuclear import and nucleosomal disruption (Malojirao et al., 2018). Its cytotoxic activity was realized via induction of apoptosis, cell cycle blockage at S-G2/M phase, activation of Bax, Bad and Cytochrome c by Bcl-2 expression neutralization, with simultaneous downregulation of PI3K/Akt survival signal, caspase-3 overexpression (by this steroidal alkaloid to cleave its substrate PARP) and nuclear import of DFF-40 promotion. The ability of steroidal alkaloids of plant origin to stimulate apoptosis processes is also evidenced by other researchers (Shiu et al., 2007).

Conclusion

Thus, in experiments *in vivo*, we have shown *Veratrum album L.* extracts clear dose-dependent clastogenic effect. The results obtained indicate the urgent need for additional assessment of herbal medicines' side effects and, first of all, those that are approved for use in children.

BIBLIOGRAPHY

Anywar G., Kakudidi E., Byamukama R., Mukonzo J., Schubert, A., Oryem-Origa H., Jassoy C. A review of the toxicity and phytochemistry of medicinal plant species used by herbalists in treating people living with HIV/AIDS in Uganda. *Frontiers in Pharmacology*. 2021. 12(615147). DOI: 10.3389/fphar.2021.615147.

Aydin T., Cakir A., Kazaz C., Bayrak N., Bayir Y., Taşkesenligil Y. Insecticidal metabolites from the rhizomes of *Veratrum album* against adults of Colorado potato beetle, *Leptinotarsa decemlineata*. *Chemistry & biodiversity*. 2014. 11(8). P. 1192–1204. DOI: 10.1002/cbdv.201300407.

Christov V., Mikhova B., Ivanova A., Serly J., Molnar J., Selenge D., Solongo A., Kostova N., Gerelt-Od Y., Dimitrov D. Steroidal alkaloids of *Veratrum lobelianum* Bernh. and *Veratrum nigrum* L. *Zeitschrift fur Naturforschung. C, Journal of biosciences*. 2010. 65(3-4). P 195–200. DOI: 10.1515/znc-2010-3-405.

Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the European Union, 2004; L 136/85-L 136/90.

Galkin O. Yu., Besarab A. B., Lutsenko T. N. Characteristics of enzyme-linked immunosorbent assay for detection of IgG antibodies specific to *Chlamydia trachomatis* heat shock protein (HSP-60). *The Ukrainian Biochemical Journal*. 2017. 89(1). P. 22–30. DOI: 10.15407/ubj89.01.022.

Galkin O. Yu., Savchenko A. A., Nikitina K. I., Dugan O. M. Obtaining and study of properties of new monoclonal antibodies against human IgE. *The Ukrainian Biochemical Journal*. 2013. 85(5). P. 81–87. DOI: 10.15407/ubj85.05.081.

Garnier R., Carlier P., Hoffelt J., Savidan A. Acute dietary poisoning by white hellebore (*Veratrum album* L.). Clinical and analytical data. A propos of 5 cases. *Annales de medecine interne*. 1985. 136(2). P. 125–128.

Gebhardt R. Antioxidative, antiproliferative and biochemical effects in HepG2 cells of a homeopathic remedy and its constituent plant tinctures tested separately or in combination. *Arzneimittelforschung*. 2003. 53(12). P. 823–830. DOI: 10.1055/s-0031-1299836.

Grigorieva S. M., Starosyla D. B., Rybalko S. L., Motronenko V. V., Lutsenko T. M., Galkin O. Yu. Effect of recombinant human interleukin-7 on *Pseudomonas aeruginosa* wound infection. *The Ukrainian Biochemical Journal*. 2019. 91(5). P. 7–15. DOI: 10.15407/ubj91.05.007.

Grobosch T., Binscheck T., Martens F., Lampe D. Accidental intoxication with *Veratrum album*. *Journal of analytical toxicology*. 2008. 32(9). P. 768–773. DOI: 10.1093/jat/32.9.768.

Grosu E., Ichim M.C. Turning meadow weeds into valuable species for the Romanian ethnomedicine while complying with the environmentally friendly farming requirements of the European Union's common agricultural policy. *Frontiers in pharmacology*. 2020. 11(529). DOI: 10.3389/fphar.2020.00529.

Holstein A. F. Reguläre und abnorme Akrosombildung beim Menschen [Regular and abnormal formation of acrosome in the human]. *Verhandlungen der Anatomischen Gesellschaft*. 1972. 67(585).

Ivanova A., Serly J., Christov V., Stamboliyska B., Molnar J. Alkaloids derived from genus Veratrum and Peganum of Mongolian origin as multidrug resistance inhibitors of cancer cells. *Fitoterapia*. 2011. 82(4). P. 570–575. DOI: 10.1016/j.fitote.2011.01.015.

Jin Z. Q., Hao J., Yang X., He J. H., Liang J., Yuan J. W., Mao Y., Liu D., Cao R., Wu X. Z., Li X., Chen D. Higenamine enhances the antitumor effects of cucurbitacin B in breast cancer by inhibiting the interaction of AKT and CDK2. *Oncology reports*. 2018. 40(4). P. 2127–2136. DOI: 10.3892/or.2018.6629.

Kayani M. A., Parry J. M. The *in vitro* genotoxicity of ethanol and acetaldehyde. *Toxicology in vitro*. 2010. 24(1). P. 56–60. DOI: 10.1016/j.tiv.2009.09.003.

Kislyak S., Dugan O., Yalovenko O. Systems for genetic assessment of the impact of environmental factors. *Innovative Biosystems and Bioengineering*. 2024. 8(2). 3–27. DOI: 10.20535/ibb.2024.8.2.288127.

Klochko V., Todosiichuk T., Lin W., Kobzysta O., Bobyr V. Antimicrobial and cytotoxic characteristics of antibiotic streptofungin. *Innovative Biosystems and Bioengineering*. 2023. 7(2). P. 13–21. DOI: 10.20535/ibb.2023.7.2.286158.

Krepkova L. V., Bortnikova V. V., Sokolskaya T. A. Some aspects of toxicological study of medicinal preparations, created on the basis of medical plant raw materials. *Fundamental research*. 2013. 9(2). P. 256–258.

Kurdil N. V., Palamar B. I., Lisovska V. S., Zhminko P. G., Balan H. M., Andryushchenko V. V. Hepatotoxic effects due to the combined consumption of opioid drugs and alcohol. *Clinical and Preventive Medicine*. 2024. 4. P. 72–77. DOI: 10.31612/2616-4868.4.2024.10.

Malojirao V. H., Vigneshwaran V., Thirusangu P., Mahmood R., Prabhakar B. T. The tumor antagonistic steroidal alkaloid Solanidine prompts the intrinsic suicidal signal mediated DFF-40 nuclear import and nucleosomal disruption. *Life sciences*. 2018. 199. P. 139–150. DOI: 10.1016/j.lfs.2018.03.015.

OECD Guideline for the Testing of Chemicals: mammalian bone marrow chromosome aberration test. 1997 Available from: http://www.oecd.org/chemicalsafety/riskassessment/1948450.pdf.

Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the pediatric population. European Medicines Agency, 2012. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-necessity-initiatives-stimulate-conduct-clinical-studies-herbal-medicinal-products-paediatric-population_en.pdf

Seale J. T., Carpenter J. E., Matthew D. Eisenstat M. D., Kiernan E. A., Morgan B. W., Nogee D. P., Pu X., Therriault C. A., Yeh M., McDougal O. M. *Veratrum parviflorum* poisoning: identification of steroidal alkaloids in patient blood and breast milk. *Clinical toxicology (Philadelphia, Pa.)*. 2022. 60(12). P. 1309–1317. DOI: 10.1080/15563650.2022.2132166.

Shevchenko O., Kuzmin O., Melnyk O., Khareba V., Frolova N., Polyovyk V. Antioxidant properties of water-alcohol infusions of tea-herbal compositions based on yerba mate. *Ukrainian Food Journal*. 2022. 11(3). P. 403–415. DOI: 10.24263/2304-974X-2022-11-3-6.

Shiu L. Y., Chang L. C., Liang C. H., Huang Y. S., Sheu H. M., Kuo K. W. Solamargine induces apoptosis and sensitizes breast cancer cells to cisplatin. *Food and chemical toxicology*. 2007. 45(11). P. 2155–2164.

Vachalkova A., Grancai D., Nagy M., Novotny L. Evaluation of potential carcinogenicity of steroidal alkaloids from *Veratrum album* L. by the DC polarography method. *Neoplasma*. 1998. 45(4). P. 243–247.

REFERENCES

Anywar, G., Kakudidi, E., Byamukama, R., Mukonzo, J., Schubert, A., Oryem-Origa, H., & Jassoy, C. (2021). A review of the toxicity and phytochemistry of medicinal plant species used by herbalists in treating people living with HIV/AIDS in Uganda. *Frontiers in Pharmacology*, *12(615147)*. DOI: 10.3389/fphar.2021.615147.

Aydin, T., Cakir, A., Kazaz, C., Bayrak, N., Bayir, Y., & Taşkesenligil, Y. (2014). Insecticidal metabolites from the rhizomes of *Veratrum album* against adults of Colorado potato beetle, *Leptinotarsa decemlineata*. *Chemistry & biodiversity*, *11(8)*, 1192–1204. DOI: 10.1002/cbdv.201300407.

Christov, V., Mikhova, B., Ivanova, A., Serly, J., Molnar, J., Selenge, D., Solongo, A., Kostova, N., Gerelt-Od, Y., & Dimitrov, D. (2010). Steroidal alkaloids of *Veratrum lobelianum* Bernh. and *Veratrum nigrum* L. *Zeitschrift fur Naturforschung. C, Journal of biosciences*, *65(3-4)*, 195–200. DOI: 10.1515/znc-2010-3-405.

Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use. Official Journal of the European Union, 2004; L 136/85-L 136/90.

Galkin, O.Yu., Besarab, A.B., & Lutsenko, T.N. (2017). Characteristics of enzyme-linked immunosorbent assay for detection of IgG antibodies specific to *Chlamydia trachomatis* heat shock protein (HSP-60). *The Ukrainian Biochemical Journal*, *89(1)*, 22–30. DOI: 10.15407/ubj89.01.022.

Galkin, O. Yu., Savchenko, A. A., Nikitina, K. I., & Dugan, O. M. (2013). Obtaining and study of properties of new monoclonal antibodies against human IgE. *The Ukrainian Biochemical Journal*, *85(5),* 81–87. DOI: 10.15407/ubj85.05.081.

Garnier, R., Carlier, P., Hoffelt, J., & Savidan, A. (1985). Acute dietary poisoning by white hellebore (*Veratrum album* L.). Clinical and analytical data. A propos of 5 cases. *Annales de medecine interne*, *136(2)*, 125–128.

Gebhardt, R. (2003). Antioxidative, antiproliferative and biochemical effects in HepG2 cells of a homeopathic remedy and its constituent plant tinctures tested separately or in combination. *Arzneimittelforschung, 53(12)*, 823–830. DOI: 10.1055/s-0031-1299836.

Grigorieva, S. M., Starosyla, D. B., Rybalko, S. L., Motronenko, V. V., Lutsenko, T. M., & Galkin, O. Yu. (2019). Effect of recombinant human interleukin-7 on *Pseudomonas aeruginosa* wound infection. *The Ukrainian Biochemical Journal*, *91(5)*, 7–15. DOI: 10.15407/ubj91.05.007.

Grobosch, T., Binscheck, T., Martens, F., & Lampe, D. (2008). Accidental intoxication with *Veratrum album*. *Journal of analytical toxicology*, *32(9)*, 768–773. DOI: 10.1093/jat/32.9.768.

Grosu, E., & Ichim, M.C. (2020). Turning meadow weeds into valuable species for the Romanian ethnomedicine while complying with the environmentally friendly farming requirements of the European Union's common agricultural policy. *Frontiers in pharmacology*, *11(529)*. DOI: 10.3389/fphar.2020.00529.

Holstein, A. F. (1972) Reguläre und abnorme Akrosombildung beim Menschen [Regular and abnormal formation of acrosome in the human]. *Verhandlungen der Anatomischen Gesellschaft* [in German].

Ivanova, A., Serly, J., Christov, V., Stamboliyska, B., & Molnar, J. (2011). Alkaloids derived from genus Veratrum and Peganum of Mongolian origin as multidrug resistance inhibitors of cancer cells. *Fitoterapia, 82(4)*, 570–575. DOI: 10.1016/j.fitote.2011.01.015.

Jin, Z. Q., Hao, J., Yang, X., He, J. H., Liang, J., Yuan, J. W., Mao, Y., Liu, D., Cao, R., Wu, X. Z., Li, X., & Chen, D. (2018). Higenamine enhances the antitumor effects of cucurbitacin B in breast cancer by inhibiting the interaction of AKT and CDK2. *Oncology reports, 40(4)*, 2127–2136. DOI: 10.3892/or.2018.6629.

Kayani, M. A., & Parry, J. M. (2010). The *in vitro* genotoxicity of ethanol and acetaldehyde. *Toxicology in vitro, 24(1)*, 56–60. DOI: 10.1016/j.tiv.2009.09.00.

Kislyak, S., Dugan, O., & Yalovenko, O. (2024). Systems for genetic assessment of the impact of environmental factors. *Innovative Biosystems and Bioengineering, 8(2)*, 3–27. DOI: 10.20535/ibb.2024.8.2.288127.

Klochko, V., Todosiichuk, T., Lin, W., Kobzysta, O., & Bobyr, V. (2023). Antimicrobial and cytotoxic characteristics of antibiotic streptofungin. *Innovative Biosystems and Bioengineering, 7(2)*, 13–21. DOI: 10.20535/ibb.2023.7.2.286158.

Krepkova, L. V., Bortnikova, V. V., & Sokolskaya, T. A. (2013). Some aspects of toxicological study of medicinal preparations, created on the basis of medical plant raw materials. *Fundamental research, 9(2)*, 256–258.

Kurdil, N. V., Palamar, B. I., Lisovska, V. S., Zhminko, P. G., Balan, H. M., & Andryushchenko, V. V. (2024). Hepatotoxic effects due to the combined consumption of opioid drugs and alcohol. *Clinical and Preventive Medicine, 4*, 72–77. DOI: 10.31612/2616-4868.4.2024.10.

Malojirao, V. H., Vigneshwaran, V., Thirusangu, P., Mahmood, R., & Prabhakar, B. T. (2018). The tumor antagonistic steroidal alkaloid Solanidine prompts the intrinsic suicidal signal mediated DFF-40 nuclear import and nucleosomal disruption. *Life sciences, 199*, 139–150. DOI: 10.1016/j.lfs.2018.03.015.

OECD Guideline for the Testing of Chemicals: mammalian bone marrow chromosome aberration test. 1997 Available from: http://www.oecd.org/chemicalsafety/riskassessment/1948450.pdf.

Reflection paper on the necessity of initiatives to stimulate the conduct of clinical studies with herbal medicinal products in the pediatric population. European Medicines Agency, 2012. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-necessity-initiatives-stimulate-conduct-clinical-studies-herbal-medicinal-products-paediatric-population_en.pdf.

Seale, J. T., Carpenter, J. E., Matthew, D., Eisenstat, M.D., Kiernan, E. A., Morgan, B. W., Nogee, D. P., Pu, X., Therriault, C. A., Yeh, M., & McDougal, O. M. (2022). *Veratrum parviflorum* poisoning: identification of steroidal alkaloids in patient blood and breast milk. *Clinical toxicology (Philadelphia, Pa.)*, *60(12)*, 1309–1317. DOI: 10.1080/15563650.2022.2132166.

Shevchenko, O., Kuzmin, O., Melnyk, O., Khareba, V., Frolova, N., & Polyovyk, V. (2022). Antioxidant properties of water-alcohol infusions of tea-herbal compositions based on yerba mate. *Ukrainian Food Journal, 11(3)*, 403–415. DOI: 10.24263/2304-974X-2022-11-3-6.

Shiu, L. Y., Chang, L. C., Liang, C. H., Huang, Y. S., Sheu, H. M., & Kuo, K. W. (2007). Solamargine induces apoptosis and sensitizes breast cancer cells to cisplatin. *Food and chemical toxicology*, *45(11)*, 2155–2164.

Vachalkovs, A., Grancai, D., Nagy, M., & Novotny, L. (1998). Evaluation of potential carcinogenicity of steroidal alkaloids from *Veratrum album* L. by the DC polarography method. *Neoplasma*, *45(4),* 243–247.

Стаття надійшла до редакції 28.06.2024.
Стаття прийнята до друку 05.08.2024.

Конфлікт інтересів: відсутній.
Внесок авторів:
Бондаренко Л.Б. – оцінка генотоксичності, аналіз отриманих даних, підготовка тексту;
Блажчук І.С. – оцінка генотоксичності, аналіз отриманих даних, підготовка тексту;
Карацуба Т.А. – аналіз отриманих даних;
Тишкін С.М. – аналіз отриманих даних;
Калачінська М.М. – оцінка генотоксичності, аналіз отриманих даних, підготовка тексту;
Сергійчук Н.М. – статистичний аналіз, аналіз отриманих даних;
Коваленко В.М. – оцінка генотоксичності, аналіз отриманих даних, підготовка тексту;
Шевчук К.М. – статистичний аналіз, аналіз отриманих даних, підготовка тексту;
Бесараб О.Б. – статистичний аналіз, аналіз отриманих даних, підготовка тексту.

Електронна адреса для листування з авторами:
tmb@lll.kpi.ua