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GENOTOXIC AND PROTECTIVE ACTIVITY OF EXTRACTS FROM *INULA BRITANNICA* (FAM. *COMPOSITAE*)) IN THE BODY OF LABORATORY MICE

The protective and mutagen-modifying activity of the complex of biologically active substances (BAS) in the extract from the underground part of the plant Inula britannica in the cells of the visceral organs of laboratory mice was studied. Alkaline variation of the comet assay was used to determine genotoxic/antigenotoxic activity. The frequency of single-stranded DNA breaks in the cells of the brain and bone marrow, lungs, heart, kidneys, liver, stomach, spleen was assessed by the following parameters: % of DNA in tail, Olive tail moment, damage index. It was found that extracts of BAS in concentrations of 100.0 mg/l and 150.0 mg/l did not show genotoxic activity, the frequency of single-strand breaks in all studied organs did not statistically significantly exceed the spontaneous level in intact animals. When exposed to asymmetric dimethylhydrazine (UDMH), the cells of the studied organs showed a statistically significant increase in the number of single-stranded DNA breaks compared to intact laboratory mice. When combined with UDMH as a positive control, extract of Inula britannica significantly reduces the genotoxic effect of xenobiotics. The frequency of DNA breaks in animals that simultaneously received UDMH and Inula britannica extract was statistically significantly lower compared with mice that received only UDMH. All this suggests the presence of antimutagenic and antigenotoxic activity in the extract of Inula britannica.

Key words: Inula britannica, biologically active substances, mutagen, antimutagen, genotoxicity, DNA comet assay.

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Британдық аңдыз (*Inula britannica* (*Compositae* тұқымдасы)) сығындысының зертханалық тышқандардың ағзасындағы генотоксикалық және қорғаушы белсенділігі

Inula Britannica өсімдігінің жерасты бөлігінен алынған сығындысын зертханалық тышқандардың висцеральды дене мүшелерінде жасушаларына антимутагенді және мутагенді белсенділігі зерттелді. Генотоксикалық немесе антигенотоксикалық белсенділікті анықтау үшін ДНК-комет әдісінің сілті вариациясы пайдаланылды. Оливе құйрық сәті, комета құйрықтағы ДНК пайызы, залал индексі параметрлер бойынша келесі 8 дене мүше жасушаларында ДНҚ үзілістерінің жиілігін бағаладық: ми және сүйек кемігі, өкпе, жүрек, бүйрек, бауыр, асқазан, көкбауыр. Биологиялық активті заттарды (БАЗ) 100.0 мг/л және 150,0 мг/л концентрациясында пайдаландық. Осы екі концентрациясында БАЗ-ды зертханалық тышқандарға ішкізкенде олардың бүкіл мүше жасушаларында ДНК үзілістер жиілігі интактты жануарлармен салыстырғанда риясыз деңгейінен айтарлықтай жоғары емес еді, демек *Inula britannica* сығындысының генотоксикалық белсенділігі табылған жоқ. Ал симметриясыз диметилгидразинді (НДМГ) қолданғанда зерттелген дене мүшелерінің жасушаларын интактты зертханалық тышқандармен салыстырғанда ДНҚ-үзілістер санының статистикалық маңызды ұлғаюы болды. НДМГ-мен БАЗ-ды бір мезгілде қолданған кезде, *Inula britannica* сығындысы ксенобиотиктердің генотоксикалық әсерін статистикалық түрде айтарлықтай азайтты. Мұның

барлығы *Inula britannica* сығындысы антимутагендік және антигенотоксикалық белсенділікті білдіретін қабілеті бар екендігін болжайды.

Түйін сөздер: британдық аңдыз, биологиялық активті заттар, мутаген, антимутаген, генотоксикалық әсер, ДНК-комета әдісі.

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Генотоксическая и протекторная активность экстрактов девясила британского (*Inula britannica* (сем. *Compositae*)) в организме лабораторных мышей

Изучена протекторная и мутаген-модифицирующая активность комплекса биологически активных веществ (БАВ) в экстракте из подземной части растения Inulabritannica в клетках висцеральных органов лабораторных мышей. Для определения генотоксической/антигенотоксической активности была использована щелочная вариация метода ДНК-комет. Оценивали частоту однонитевых разрывов ДНК в клетках головного и костного мозга, легких, сердца, почках, печени, желудка, селезенки по параметрам: %ДНК в хвосте кометы, момент хвоста по Оливе, индекс повреждения. Установлено, что экстракты БАВ в концентрациях 100,0 и 150,0 мг/л не проявили генотоксической активности, частота однонитевых разрывов во всех изученных органах статистически значимо не превышала спонтанного уровня у интактных животных. При воздействии несимметричного диметилгидразина (НДМГ) в клетках изучаемых органов наблюдалось статистически значимое увеличение количества однонитевых разрывов ДНК по сравнению с интактными лабораторными мышами. При совместном действии с НДМГ в качестве положительного контроля экстракт Inulabritannicaсущественно модифицировал генотоксический эффект ксенобиотика в сторону его снижения. Частота разрывов ДНК у животных, которые одновременно получали НДМГ и экстракт Inulabritannica, была статистически значимо ниже по сравнению с мышами, получавшими только НДМГ. Все это позволяет предполагать наличие антимутагенной и антигенотоксической активности у экстракта Inula britannica.

Ключевые слова: девясил британский, биологически активные вещества, мутаген, антимутаген, генотоксичность, метод ДНК-комет.

Abbreviations

PAHs – polycyclic aromatic hydrocarbons; BAS – biologically active substances; UDMH – unsymmetrical dimethylhydrazine; OTM – Olive tail moment; %DNA – "% DNA in tail; DI – damage index.

Introduction

Recently, due to the increase of anthropogenic pressure on the environment, the issue of protecting the population from the negative impact of environmentally hazardous factors has emerged. Due to the activity of industrial enterprises, automobile, the anthropogenic impact on the environment growing every year and the biosphere is rapidly accumulating chemical compounds with genotoxic properties [1-6]. A number of authors have shown mutagenic and carcinogenic activity for PAHs, alkylating compounds, a number of heavy metals, organochlorine and organophosphorus pesticides, nitroso compounds, and some plant secondary compounds [6–9]. Environmental pollution by mutagens of a physical, chemical and biological nature facilitates to the development of many chronic diseases, including oncological ones. Therefore, the search for protectors from the mutagenic, genotoxic and toxic effects of environmental pollutants is relevant. Plant are the promising sources of antimutagens that reduce mutations. Plants contain a variety of biologically active substances (BAS), such as vitamins, saponins, glycopeptides, amino acids, flavonoids, coumarins, flavones, terpenoids, which have complex therapeutic effect and antioxidant properties [10-15]. In addition, plants are an affordable and rapidly renewable resource.

In the flora of Kazakstan are about 6000 species of higher strata, 1406 of them are medicinal, but only 230 species of these plants are used in official medicine. These medicinal plants contain most of the known classes of biologically active substances. Among them prevail the species containing flavonoids and their derivatives (60% of species), alkaloids (42%), organic and phenolic acids (34%), vitamins (32%), tannins (29%), coumarins

(25%) and other biologically active substances. In accordance with the phytochemical composition, medicinal plants in Kazakhstan have a very broad spectrum of pharmacological action [16].

One of the widely used medicinal plants is *Inula britannica* L., from the genus *Inula*, subfamily *Asteraceae*, family *Compositae*. In Kazakhstan *Inula britannica* grows everywhere, with the exception of highlands. The underground and above-ground parts of the *Inula Britannica* contain such bioactive substances as essential oils, sesquiterpenes, alkaloids, tannins, saponins, phenol carboxylic acids, coumarins, flavonoids, steroids, etc. [17-19]. All of the above suggests that *Inula britannica* is a promising plant for obtaining new phytodrugs [20-21].

In this regard, the purpose of this study was to study the mutagenic and protective activity of extract from the underground part of the *Inula britannica* (fam. *Compositae*)) in the body of laboratory mice.

Materials and methods

The extract from the underground part of *Inula britannica* L. (Fam. *Compositae*) in concentrations of 100 and 150 mg / kg was tested to the antimutagenic and mutagenic activity.

An aqueous solution of asymmetric dimethyl hydrazine (UDMH) was used as a positive control. It is known that UDMH is a highly toxic compound [23-26] and has pronounced mutagenic effect [25].

As an object white laboratory mice of BALB/c line (*Mus Musculus* Linn.) were used. Laboratory mice are widely used to evaluate the efficacy and toxicity of various xenobiotics and drugs [22].

In total, 30 laboratory mice at age of 2-3 months were used in the experiment. The animals were subjected to acute separate and combined exposure to asymmetric dimethylhydrazine at a dose of 6.6 mg/kg and to extracts of biologically active substances from the underground part of *I. britannica* at doses of 100 and 150 mg / kg. Extracts of *I. britannica* were administered orally, and UDMH was administered intraperitoneally. 24 hours after the administration of the substances, the animals were killed. All animals were divided into 6 groups of 5 mice each: I – intact animals; II -animals treated with UDMH at a dose of 6.6 mg / kg once; III, IV – animals that received the extract of BAS *I.britannica* in doses of 100 and 150 mg / kg, respectively; V, VI – animals that received join UDMG at a dose of 6.6 mg / kg and extracts of BAS *I.britannica* at doses of 100 and 150 mg / kg, respectively. The dose of UDMH was chosen based on the available information about LD50 for mice – 132.0 mg / kg for intraperitoneal admnistration. The animals were carried out according to international standards [27].

To determine the genotoxic/antigenotoxic effect of the compounds the DNA comet assay (alkaline variation) was used. 8 organs of mice were examined – bone and brain, stomach, kidneys, liver, spleen, lungs and heart [28]. At least 100 photos of DNA comets were taken from each preparation. At each point of the experiment were analyzed at least 500 "DNA comets".

The following parameters were calculated: "the percentage of DNA in the tail" (%DNA in tail) and the "Olive tail moment" (OTM). The Casp 1.2.2 software (CASPlab, Wroclaw, Poland) was used. The parameter "percentage of DNA in the tail of a comet" is the number of single-stranded fragments that were formed as a result of breaks and the realization of alkaline-DNA segments and migrated towards the anode during electrophoresis. "Olive tail moment" is the distance from the center of the nucleus to the center of the comet's tail density multiplied by "% DNA in the comet's tail". The DNA damage index (DI) determines the degree of genotoxic effect of any factor and is calculated by dividing "%DNA in tail" (or "Olive tail moment") in the experimental group on "%DNA in tail" (or "Olive tail moment") in the control group. The factor has a pronounced genotoxic property when the damage index exceeds 2.0 [28].

Statistical processing of the results was performed in the Data Analysis add-in Microsoft Excel and StatPlus5Pro version 6 (Analyst Soft Inc., USA). In all cases, mean values and mean errors were determined. The significance of differences between averages was evaluated by Student's t test, the differences were considered reliable at a confidence level of 0.95 ($p < 0.05$).

Results and discussion

Alkaline variation of DNA comets allows to register single-strand breaks in DNA. In this study, DNA breaks in the cells of 8 organs of mice — the bone marrow, brain, stomach, kidneys, liver, spleen, lungs, and heart — were analyzed (Table 1, 2).

BAS from the underground part of *I.britannica* in doses of 100.0 and 150.0 mg/l induced in the brain cells of mice DNA breaks at the level of control according to the parameters "% DNA in tail" (%DNA) and "Olive tail moment" (OTM). UDMH, which has mutagenic activity, induced in the brain cells the number of DNA breaks with a frequency exceeding the control level. In the group

with combined effects of BAS and UDMH in doses of 100.0 and 150.0 mg / l, the frequency of single-stranded DNA breaks in the brain cells of mice in %DNA decreased 1.89 ($p < 0.05$) times and 1.95 ($p < 0.05$) times according to %DNA, and according to the OTM – 2.51 ($p < 0.05$) and 2.91 times ($p < 0.05$) in comparison with the positive control, respectively. The damage index (DI) when exposed to BAS in doses of 100.0 and 150.0 mg/l was 1.37 and 1.45 by parameter %DNA, and according to the OTM – 1.06 and 1.17, respectively. DI in the brain cells of mice when exposed to UDMH was 3.33 and 3.70, for the parameters % DNA and OTM, respectively. With the combined effect of BAS and UDMH, DI amounted to 1.76 and 1.71 by parameter %DNA, and 1.48 and 1.27 by OTM, respectively.

In the cells of the heart, the number of DNA breaks with the intoxication of biologically active substances in both doses was at the level of control by parameters %DNA and OTM.

As a result of the intoxication mice by UDMH, the number of single-stranded DNA breaks in the heart cells was statistically significantly increased, according to %DNA 5.93 ± 0.45, and according to OTM – 1.63 ± 0.14. With the joint action of BAS and UDMH, a decrease in the values of the studied parameters was observed. So, the BAS in the dose of 100.0 mg/l reduced the DNA breaks induced by UDMH by 1.52 times ($p < 0.05$) according to %DNA and by 1.35 times ($p < 0.05$) to OTM, and the BAS in the dose of 150 mg/l – 1.74 times ($p < 0.05$) by %DNA and 1.55 times by OTM. DI when exposed to *I.britannica* in doses of 100.0 and 150.0 mg/l amounted to 1.12 and 1.19 by %DNA, and according to OTM by 1.08 and 1.21 times. When exposed to UDMH, DI was 2.20 by %DNA and 2.04 in terms of the OTM, respectively. With the combined effect of biologically active substances at doses of 100.0 and 150.0 mg/l and UDMH DI was, respectively, 1.45 and 1.27 according to %DNA, and to OTM – 1.51 and 1.31.

A similar pattern was observed for the liver cells of mice that took the BAS and UDMH separately and together. The frequency of breaks in groups III and IV was at the control level. UDMH induced in the liver cells of mice (group II) DNA breaks with a frequency significantly higher than the control level. With the combined effect of BAS and UDMH, BAS significant decreased the genotoxic effect of xenobiotics. Thus, in in the liver cells of animals of V and V groups, the frequency of single-stranded DNA breaks significantly decreased as compared with mice intoxicated with UDMH by 1.68 ($p < 0.05$) and 1.82 ($p < 0.05$) times for the parameter % DNA, and 1.84 ($p < 0.05$) and 1.57 times for the parameter OTM – ($p < 0.05$), respectively. DI in the liver cells of mice of groups III and IV, according to %DNA, was 1.17 and 1.25, and according to OTM, it was 1.07 and 1.26. When exposed to UDMH, DI in animals of group II was 2.55% by % DNA, and 2.1% by OTM. With the combined effect of a BAS with UDMH (Group III and IV), the DI by %DNA was 1.49 and 1.37, and in the OTM, it was 1.16 and 1.36, respectively.

In the kidney cells of mice of III and IV, groups the number of DNA breaks was at the level of control in both studied parameters. UDMH induced single-strand DNA breaks in the kidney cells of mice (group II) with a frequency significantly higher than the spontaneous level. In III and IV groups, the joint effect of BAS and UDMH reduced the frequency of single-stranded DNA breaks as compared with group II animals intoxicated with UDMH. So, with a dose of 100 mg/l BAS, the reduction amounted 2.12 ($p < 0.05$) and 2.38 ($p < 0.05$) times according to %DNA and OTM, respectively, and at 150.0 mg/l – 2.07 ($p < 0.05$) and 2.34 ($p < 0.05$) times, respectively. DI in the kidney cells when exposed to I.britannica in doses of 100.0 and 150.0 mg/l according to OTM was 1.07 and 1.14, and to %DNA – 1.04 and 1.15. DI when exposed to UDMH by parameters %DNA and OTM was 3.29 and 4.19, respectively. With the combined effect of biologically active substances in doses of 100.0 and 150.0 mg/l with UDMH, the damage index by parameter %DNA was 1.55 and 1.59, by parameter OTM – 1.76 and 1.79, respectively.

The same picture was shown for the lung cells. In the experiment with the introduction of biologically active substances, the number of DNA breaks was at the level of control by parameters % of DNA in tail and Olive tail moment. With the introduction of UDMH, the number of DNA breaks has statistically significantly increased as compared with the control and with groups of animals that took BAS.

When BAS combined with UDMH, the frequency of single-stranded DNA breaks in lung cells was statistically significantly reduced in contrast with mice intoxicated with UDMH. So, at a dose of 100.0 mg / l, this decrease amounted 1.87 ($p < 0.05$) times by parameter % of DNA in tail and 1.65 ($p < 0.05$) times by Olive tail moment. At a dose of 150.0 mg/l, the decrease amounted by 1.89 ($p < 0.05$) times according to %DNA and 1.93 times ($p < 0.05$) according to the OTM. DI in the lungs cells of mice when exposed to UDMH was 2.80 and 2.74, by parameters %DNA and OTM, respectively. The DI in lung cells when taken in

mice with BAS at doses of 100.0 and 150.0 mg/l was 1.17 and 1.30 for % DNA, and 1.06 and 1.33 for OTM, respectively. DI with the combined effect of BAS and UDMH was 1.50 and 1.48 according to %DNA, and in the case of OTM – 1.67 and 1.42 times, respectively.

Table 1 – The frequency of DNA breaks in the cells of organs of mice with separate and joint effects of UDMH and the complex of biologically active substances from Inula britannica by parameter "% DNA in the comet's tail"

Variant	The frequency of DNA breaks in the cells of various organs by parameter «%DNA in tail» (%DNA)							
	brain	heart	liver	kidneys	lungs	bone marrow	stomach	spleen
I – control	2,30 ± 0,35	2,69 ± 0,20	2,83 ± 0,37	2,49± 0,19	2,09 ± 0,38	2,20 ± 0,32	1,97 ± 0,31	2,65 ± 0,37
II – UDMH 6,6 mg/kg	7,67 ± 0,58*	5,93 ± 0,45*	7,08 ± 0,42*	8,19± 0,51*	5,86 ± 0,32*	5,98 ± 0,44*	4,12 ± 0,17*	5,75 ± 0,16*
III – BAS 100 mg/kg	3,16 ± 0,33	3,02 ± 0,24	3,31 ± 0,29	2,58± 0,19	2,44± 0,19	2,60 ± 0,28	2,39 ± 0,14	3,14 ± 0,25
IV – BAS 150 mg/kg	3,34 ± 0,42	3,20 ± 0,37	3,53 ± 0,19	2,86± 0,25	2,72± 0,24	2,84 ± 0,26	2,53 ± 0,25	3,23 ± 0,20
V – UDMH + BAS, 100 mg/kg	4,05 ± 0,21•	3,89 ± 0,29•	4,22 ± 0,22•	3,86± 0,28•	3,14± 0,33•	3,87 ± 0,31•	3,05 ± 0,15•	3,65 ± 0,20•
VI – UDMH + BAS, 150 mg/kg	3,94 ± 0,23•	3,41 ± 0,25•	3,89 ± 0,24•	3,95± 0,20•	3,10± 0,40•	3,33 ± 0,42•	2,87 ± 0,14•	3,53 ± 0,21•
Note – * – $p<0,05$ in comparison with control values; • – $p<0,05$ in comparison with UDMH								

In bone marrow cells under the influence of biologically active substances, the frequency of DNA breaks by the parameters %DNA and OTM was at the control level. The number of single-stranded DNA breaks was statistically significantly higher compared to the control when UDMH was administered. The combined effect of BAS with UDMH reduced the frequency of DNA breaks induced by UDMH. Thus, a BAS at a dose of 100.0 mg / l reduced the number of single-strand breaks by 1.55 times ($p <0.05$) and 1.42 times ($p <0.05$) for parameters % DNA and OTM, respectively. BAS at a dose of 150.0 mg/l reduced the frequency of DNA breaks in comparison with the positive control of 2.07 ($p <0.05$) and 2.15 ($p <0.05$) times for the parameters %DNA and OTM, respectively. Damage index in bone marrow cells when exposed to biologically active substances in doses of 100.0 and 150.0 mg/l, according to % of DNA in tail of comet was 1.18 and 1.29; according to the Olive tail moment – 1.21 and 1.49. When exposed to UDMH, DI was 2.72 and 3.84, respectively, according to % of DNA and OTM. With the combined effect of BAS and UDMH, DI was 1.76 for the dose of 100 mg / l and 1.51 for the dose of 150 mg/l by parameter %DNA, and 1.86 and 1.78 for the parameter OTM, respectively.

The exposition the extract of Inula britannica show the same pattern in the stomach cells: the frequency of DNA breaks was at the level of control in both studied parameters. When exposed to UDMH, the number of DNA breaks increased as compared with the control and the amount of %DNA and OTM was 4.12 ± 0.17 and 1.52 ± 0.03, respectively. The combined effect of biologically active substances in doses of 100.0 and 150.0 mg/l with UDMH reduced the frequency of single-strand breaks in the both parameters and amounted to 3.05 ± 0.15 and 2.87 ± 0.14% according to %DNA, and according to OTM – 0.88 ± 0.05 and 0.83 ± 0.05, respectively. The DI in the stomach cells of mice, when exposed to the extract of biologically active substances in doses of 100.0 and 150.0 mg/l, was 1.21 and 1.28 by %DNA and by OTM – 1.23 and 1.28. DI with the introduction of UDMH was 2.09 by %DNA and by OTM – 2.49. DI with the combined effect of BAS with UDMH was 1.55 and 1.46 by %DNA, according to OTM – 1.44 and 1.36, respectively.

BAS in both studied doses caused the frequency of DNA breaks at the control level in the spleen cells. With the introduction of UDMH, the number of single-strand DNA breaks increased and amount to 5.75 ± 0.16 by % DNA, and 1.86 ± 0.07 by OTM. The combined effect of BAS at a dose of 100.0 mg/l with UDMH reduced the frequency of single-strand breaks by 1.57 times ($p <0.05$) and 1.84 times ($p <0.05$), respectively, according to the parameters %

DNA and OTM compared with positive control. The joint action of biologically active substances in a dose of 150.0 mg/l with UDMH reduced the frequency of DNA breaks by 1.63 times (p <0.05) and 1.86 times (p <0.05), respectively, according to % DNA and OTM. DI in the spleen cells of mice exposed to BAS in doses of 100.0 and 150.0 mg/l was 1.18 and 1.22 by % DNA; according to OTM – 1.04 and 1.07. DI when exposed to UDMH was 2.17 by % DNA, and 2.07 by OTM. With the combined effect of BAS with UDMH, DI was 1.38 and 1.33 by % DNA, according to OTM – 1.12 and 1.11, respectively.

Table 2 – The frequency of DNA breaks in the cells of organs of mice with separate and joint effects of UDMH and the complex of biologically active substances from Inula britannica by parameter "Olive tail moment"

Variant	The frequency of DNA breaks in the cells of various organs by parameter «Olive tail moment» (OTM)							
	brain	heart	liver	kidneys	lungs	bone marrow	stomach	spleen
I – control	0,88 ± 0,05	0,80 ± 0,07	0,89 ± 0,07	0,72 ± 0,07	0,66 ± 0,11	0,70 ± 0,07	0,61 ± 0,04	0,90 ± 0,07
II – UDMH 6,6 mg/kg	3,26 ± 0,27*	1,63 ± 0,14*	1,90 ± 0,12*	3,02 ± 0,35*	1,81 ± 0,11*	2,69 ± 0,21*	1,52 ± 0,03*	1,86 ± 0,07*
III – BAS 100 mg/kg	0,93 ± 0,05	0,86 ± 0,08	0,95 ± 0,06	0,77 ± 0,07	0,70 ± 0,05	0,85 ± 0,10	0,75 ± 0,09	0,94 ± 0,07
IV – BAS 150 mg/kg	1,03 ± 0,06	0,97 ± 0,09	1,12 ± 0,05	0,82 ± 0,08	0,88 ± 0,14	1,04 ± 0,09	0,78 ± 0,11	0,96 ± 0,07
V – UDMH + BAS, 100 mg/kg	1,30 ± 0,11•	1,21 ± 0,11•	1,03 ± 0,06•	1,27 ± 0,07•	1,10 ± 0,19•	1,30 ± 0,19•	0,88 ± 0,05•	1,01 ± 0,07•
VI – UDMH + BAS, 150 mg/kg	1,12 ± 0,07•	1,05 ± 0,09•	1,21 ± 0,06•	1,29 ± 0,05•	0,94 ± 0,15•	1,25 ± 0,18•	0,83 ± 0,05•	1,00 ± 0,07•
Note – * – p<0,05 in comparison with control values; • – p<0,05 in comparison with UDMH								

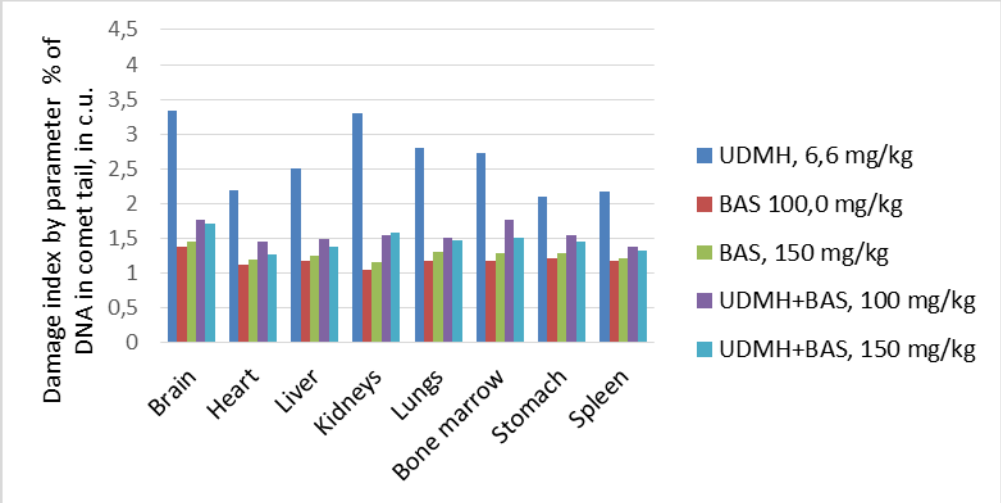

Figure 1 – The index of damage to the genotoxic effect on the cells of the organs of mice with separate and combined effects of I.britannica and UDMH (by parameter "% DNA in tail")

DNA comet assay method did not reveal the genotoxic activity of extracts from the underground part of Inula britannica in the body of laboratory mice. The frequency of single-strand breaks in the cells of the visceral organs of mice treated with aqueous solutions of extracts at concentrations of 100 mg / l, 150 mg / l was at the control level.

Using the comet assay, a pronounced genotoxic effect of asymmetric dimethylhydrazine has been established. When exposed to UDMH, there was

shown a statistically significant increase in single-strand DNA breaks in the cells of the organs studied compared with intact animals. According to the DNA-damaging effect of UDMH, the studied organs can be arranged in the following order: kidneys <brain <bone marrow <lungs <liver <stomach <heart <spleen (Figure 1, 2).

The frequency of single-stranded DNA breaks in the cells of various organs in mice susceptible to the co-effect of the biologically active substances from *I.britannica* and UDMH was statistically significantly lower compared with mice that were intoxicated with only UDMH. The organs studied are sensitive to the DNA-damaging effects of the combined effect of *I.britannica* in the used doses and UDMH can be arranged in the following order: bone marrow <kidney <brain <lungs <stomach <heart <liver <spleen (Figure 1, 2).

Thus, as a result of the conducted research, the antigenotoxic effect of extracts of biologically active substances from the underground part of *I. britannica* was established.

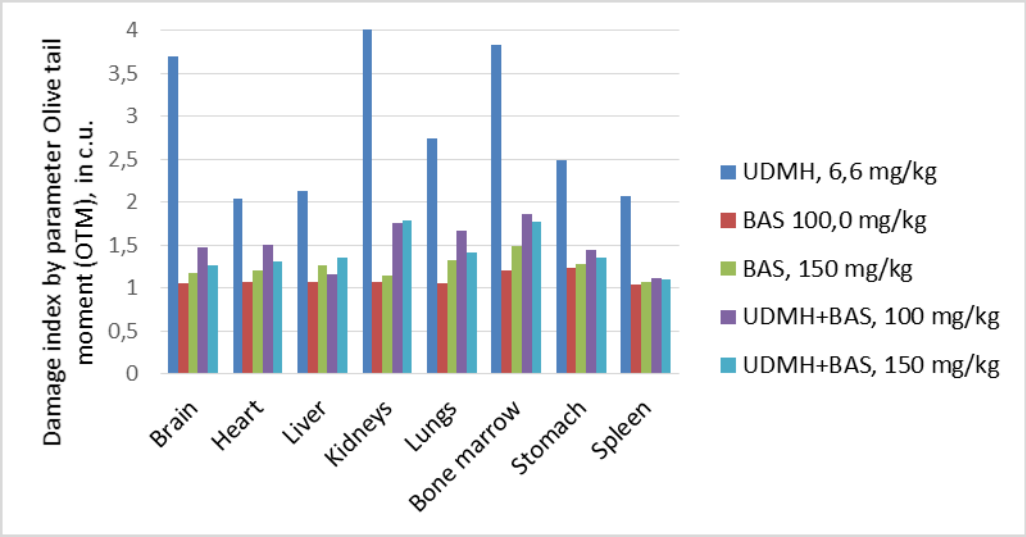

Figure 2 – The index of damage to the genotoxic effect on the cells of the organs of mice with separate and combined effects of I.britannica and UDMH (by parameter «Olive tail moment»)

Conclusion

Due to the large-scale environmental pollution of environmentally dangerous factors with toxic, genotoxic and mutagenic activity, it becomes urgent to search for effective protector action. Plants are promising sources of natural compounds with biological activity. They contain biologically active substances such as vitamins, saponins, glycopeptides, amino acids, flavonoids, coumarins, flavones, terpenoids, with pronounced antioxidant properties.

As noted earlier, one of the widely used medicinal plants is elecampane (*Inula britannica* L.). It is widely distributed in Kazakhstan, it grows almost everywhere, with the exception of highlands. *Inula britannica* contains essential oils, sesquiterpenes, alkaloids, tannins, saponins, phenolcarboxylic acids, coumarins, flavonoids, steroids, and other compounds that have high biological activity [17-19].

All the organs of this plant contain alkaloids, carbohydrates and essential oils. Roots and rhizomes contain inulin (30–40%), alkaloids (0.063–0.075%), saponins, sesquiterpenoids, tannins, and essential oils (up to 3%) [17].

A number of vitamins are known to be strong antioxidants and are able to neutralize the superoxide radical to hydrogen peroxide [10, 31]. A number of studies have shown that many vitamins have antimutagenic properties [10, 29, 31]. Thus, vitamins A, C and E reduced the mutagenic effect of methylazoxymethanol in the Ames test [10], β-carotene reduced the clastogenic effect of dioxidine and cyclophosphamide in the body of laboratory mice [29]. Another group of biologically active substances – phenolic compounds also possess antioxidant activity [30]. It was found that such phenolic compounds as epicatechin, (-) – epicaellatallatum, (-) – epigallocatechin, (-) – epigallocatehingallat, are responsible for the antimugenic activity of green and black tea

in the Ames test. Phenolic compounds present in turmeric and cloves, namely curcumin and eugenol, inhibit the mutagenic effect of N-methyl-N'-nitro-N-nitrosoguanidine in the Ames test using strains S. typhimurium TA100 and TA1535 [10]. In addition to a wide range of biological activities, flavanoids also have antimutagenic properties. All flavones and many flavonoids with a phenolic hydroxyl group (leutolin, kaemperol), chalcones and dihydrochlorins are powerful antimutagens. Citrus juice flavonoids have anti-carcinogenic and antimutagenic properties. Such flavonoids, such as glaberin from *Glycyrrhiza glabra*, quercetin, myricitin, kamferol, hesperidin from Ocimumjavonica, showed antimutagenic activity in the Ames test [10]. The anticarcinogenic and antimutagenic potential of tannins is associated with their antioxidant activity. The antimutagenic effect of tannic acid has been demonstrated in vivo using a micronucleus test. Thus, it was found that the frequency of micronucleus induced by mitomycin C, ethyl nitrosourea and 4-nitroquinolin-1-oxide in mouse bone marrow cells decreased when oral tannin acid was taken 6 hours before mutagen injection. Also, antimutagenic effects have (+) – catechin, ellagic and gallic acids [10]. Saponins have a broad spectrum of pharmacological action. Four saponins from *C. arvensis* and three saponins from *H. helix* showed antimutagenic activity against benzo (a) pyrene in the modified Ames test method [10]. Essential oils can also exhibit antimutagenic, antioxidant activities. For example, the essential oil of rosemary medicinal *Rosmarinus officinalis* has antibacterial, cytostatic, antimutagenic, antioxidant, anti-inflammatory properties [32]. Phytocompounds have an important influence on the metabolism and neutralization of foreign substances, including carcinogens and mutagens. They have the ability to bind free radicals and reactive metabolites of foreign substances, inhibit xenobiotic activating enzymes, and activate detoxification enzymes [33]. A comprehensive study of phyto compounds as potential protectors in the toxic, genotoxic and mutagenic effects of various environmental pollutants on the body is necessary.

Based on our results, we can draw the following conclusions:

- the extract from the underground part of the *Inula britannica* did not show genotoxic activity in the organism of laboratory animals. The frequency of single-stranded DNA breaks did not exceed the spontaneous level of breaks in intact animals;

- UDMH causes single-stranded DNA breaks in the cells of various organs of laboratory mice with a frequency that is significantly higher than the spontaneous level. Organ-specificity to its genotoxic effect was revealed, the kidneys were the most sensitive to the DNA-damaging effects of xenobiotics, and the spleen was the least sensitive;

- extract of *I.britannica* when used together with UDMH significantly modified the genotoxic activity of xenobiotic. The frequency of single-strand breaks in animals that simultaneously received UDMH and BAS extract was statistically significantly lower compared with mice that received only UDMH, which indicates the presence of the protective properties of BAS from the underground part of *I. britannica*.

Thus, the gene-protective effect of the studied extract of *Inula britannica* may be due to the antioxidant effect of the biologically active substances contained in the underground part of *I.britannica*, listed above.

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