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THE ANTIMUTAGENIC POTENTIAL OF BIOLOGICALLY ACTIVE COMPOUNDS OF INULA BRITANNICA L. FAMILY COMPOSITAE

Cytogenetic and mutagen-modified effects of biologically active compounds (BAC) of *Inula britannica* L. extracts from both shoots and roots parts were investigated testing on count chromosome abnormalities of cells of barley root meristem. It was established that plant extracts in concentrations 50.0 and 100.0 mg/l decrease the level of spontaneous mutagenesis in root meristem of barley.

The combined exposure of seeds to methyl methanesulfonate (MMS) and extracts independently on treatment sequence result in statistically significant reduce of MMS-induced mutagenesis. The data obtained testify to the presence of antimutagenic effect in studied extracts. There was revealed no differences in gene protective effect of whether aboveground or underground parts of *I.britannica* despite on greater content of BAC in underground part.

Key words: Inula britannica, biologically active compound, extract, mutagen, antimutagen, chromosomal aberration.

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Антимутагенный потенциал биологически активных веществ из растений *Inula britannica* l. семейства *Compositae*

Изучена цитогенетическая и мутаген-модифицирующая активность комплекса биологически активных веществ (БАВ) в экстрактах надземной и подземной частей растений *Inula britannica* с использованием теста по учету хромосомных аберраций в клетках корневой меристемы семян ячменя. Установлено, что растительные экстракты в концентрациях 50,0 и 100,0 мг/л не проявили мутагенной активности, а, наоборот, несколько снизили уровень спонтанного мутагенеза в корневой меристеме ячменя. В результате комбинированного воздействия метилметансульфоната (ММС) и растительных экстрактов вне зависимости от последовательности обработки происходило статистически значимое снижение уровня индуцированного ММС мутагенеза (указать проценты). Полученные результаты демонстрируют наличие антимутагенных свойств у изучаемых экстрактов. Нами не обнаружено статистически значимых различий в генопротекторной активности экстрактов из подземной и надземной частей девясила британского, несмотря на большее содержание БАВ в подземной части растений.

Ключевые слова: девясил британский, биологически активные вещества, экстракт, мутаген, антимутаген, хромосомные аберрации.

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Inula britannica L. туыс *Compositae* өсімдігінің биологиялық белсенді заттарының антимутагендік потенциалы

Inula britannica өсімдігінің жер асты және жер үсті бөлімдерінен алынған биологиялық белсенді заттардың (ББЗ) цитогенетикалық және мутаген-модифицирлеуші белсенділігі арпа ұрық тамыршаларының меристемалық аймағындағы хромосомалық аберрацияларды анықтау тесті көмегімен зерттелді. Өсімдік сығындылары 50,0 және 100,0 мг/л концентрацияда мутагендік белсенділік көрсетпеді, керісінше арпа ұрық тамыршаларының меристемалық аймағындағы спонтанды мутагенездің деңгейін төмендеткені анықталды. Метилметансульфонат (ММС) пен өсімдік сығындыларының аралас әсер етуі нәтижесінде ММС индуцирленген мутагенез деңгейі төмендеді. Алынған нәтижелер зерттеліп отырған сығындылардың антимутагендік қасиеттерге ие екендігін көрсетеді. Жер асты бөлімінде ББЗ мөлшер жоғары болғанына қарамастан, жер асты және жер үсті бөлімдерінен алынған сығындылардың генопротекторлық белсенділігінің статистикалық маңызды айырмашылықтары анықталмады.

Түйін сөздер: британдық андыз, биологиялық белсенді заттар, экстракт, мутаген, антимутаген, хромосомдық аберрациялар.

Introduction

The modern period of biosphere development is characterized by global pollution of environment caused by intensive economical activity. Thus the mutagenic factors of various kinds persist in humane environment a lot of which has ability to increase the optimal level of mutation that is established throughout evolutional process for every species including human beings. The radical method to cease chemical mutagenesis is to eliminate compounds with enhanced mutagenic potential out of environment. However it is not possible for several reasons and there still is human activity related to direct contact with chemical and physical mutagens. Therefore the search for pharmaceutical substances for protection of hereditary structures from various genotoxicants and prophylaxis of mutagenesis is of great interest (Vasilyeva, 2009: 659-662; Zasukhina, 2008: 464-473; Goncharova, 2005: 19-32).

Intensive researches on mutagenesis may lead to the creation of new methods of prophylaxis of hereditary diseases and congenital malformations. Recently the biologically active compounds (BAC) were at the focus of antimutagenic investigations. The majority of BAC have low toxicity and allergenicity (Durnev, 2008: 307-312; Uzun, 2007: 1903-1908; Cariño-Cortés, 2007: 691–697; Sarac, 2014: 60–64; Kumar, 2014: 815–826; Agabeili, 2012: 267-273). All BAC are related to products of secondary metabolism whereas proteins, carbohydrates and fats are considered to be primary metabolic products. But BAC exactly determine the probability of organism survival in extreme conditions. Phytocompounds are intensively studied as factors playing the key role in prophylaxis of main chronic diseases. They influence metabolic processes and participate in detoxication of xenobiotics account for cancer and mutagenesis. BAC are able to bind free radicals and reactive metabolites of foreign compounds, inhibit xenobiotic-activating enzymes and activate enzymes of detoxication (Petrov, 2008: 224).

Plants are the source of various biologically active compounds among them are vitamins, polyphenols, glycopeptides, aminoacids, sulfides, saponins, polysaccharides, terpenoids, isoflavones, indoles etc. the majority of BAC have antimutagenic, antioxidant, anticancerogenic and immunomodulating activity (Al-Jaber, 2011: 293–307; Rice-Evans, 2001: 797–807; Havsteen, 2002: 67–202; Lin, 2008: 634–646; Middleton, 2000: 673–751; Lotito, 2000: 151–157; Hernes, 2001: 3109–3122; Milner, 2001; 1027–1031; Sprygin, 2006: 81-90; Miller, 2000: 312S–319S; Ajith, 2008: 24-28; Manjula, 2006: 113-116; Farghalaly, 2009: 1-7; Sram, 2012: 39–49; Santos-Cervantes, 2007: 71-77).

Among the plants of Kazakhstan more than 100 herb species are considered to be medicinal. Gender *Inula* family *Compositae* is the focus of interest comprising high contents of polysaccharides, aminoacids, vitamins, tannins, saponin and flavonoids known to possess antioxidant effect (Mamurova, 2009: 105-107). Since it is well known that a lot of antioxidants have antimutagenic activity the aim of current study was to research antimutagenic effect of *Inula britannica* L. (fam. *Compositae*) extracts from both shoot and root parts that are source of biologically active compounds.

Materials and methods

The seeds of spring barley (*Hordeum vulgare* L.) Baisheshek variety attributed to Almaty region was used as the test object for the current research. The barley initially has low frequency of spontaneous mutation and at the same time is highly susceptible to chemical exposure, thus it is of great interest as test object of the indication of xenobiotics impact (Geras'kin, 2008: 55-56).

To assess antimutagenic activity of BAC in extracts of aboveground or underground parts of *Inula britannica* L., сем. *Compositae* the aqueous solutions were used in concentrations 50.0 and 100.0 mg/l. The positive control was aqueous solution of methyl methanesulfonate in concentration 5.0 mg/l, the distilled water was used as negative control. Seeds were treated (soaked) in appropriate solution for 4 hours, then washed, slightly dried and germinated in Petri dishes on filter paper wetted with dH_2O at t = 25 ± 1°C in incubator.

Mutagenic and antimutagenic effects of plant extracts studied were determined using test on chromosomal aberrations count (metaphase method). To prepare temporary crushed cytological preparations and to carry out cytogenetic analysis the traditional methods were used (Pukhal'skiy, 2004: 33). For cytogenetic analysis 3 hours prior to first fixation sprouting seed were transferred in 0.01% colchicine solution to accumulate metaphase plates. Main roots were fixed in the mixture of ethyl alcohol and ice acetic acid (3:1). Roots were subjected to cool hydrolysis with diluted HCl (1:1) and stained with 0.54% aqueous solution of acid fuchsin sulfite. In all variants 4 fixations were carried out with 3 hour interval. Stained roots were washed out in three portions of freshly prepared sulphureous water after that the enzymatic maceration was conducted with cytase for 40-60 min for the degradation of extracellular matrix and cell wall. Cytological preparations were placed in freezing camera at -74±1°C for 24 h. Than the frozen preparation was released form covering slide and processes in the raw of alcohols of ascending strength for dehydration and obtaining constant preparations.

The analysis of chromosomal aberrations in the cell of root embryonic meristem was conducted using digital microscope Olympus BX 43F (Olympus, Japan). In analysis there were included not only the total number of aberrations but all types of chromosomal aberrations. In each test variant 400 to 500 metaphases were calculated. Statistic data processing was carried out with standard methods using Student's test. In all cases the mean and standard deviation were calculated (Lakin, 1990: 352).

Results and discussion

Recently it was established that extracts of both shoot and root parts of *I. britannica* containing biologically active compounds do not possess mutagenic effect when testing on barley seeds as test-object. Mutation level in barley seeds treated with plant extracts does not exceed control indices (Kolumbayeva, 2016: 134-145). It is well known, that many antioxidants including some BAC possess antimutagenic activity. Therefore we had conducted the experimental research of antimutagenic activity of extracts of *Inula britannica* (table). The frequency of aberrant cells in negative control group was 1.67% (spontaneous mutation level). The comparative analysis of the frequency of aberrant cells and chromosome aberrations per 100 metaphases in barley seeds treated with whether dH_2O or BAC extracts has not revealed any statistically significant differencies. Moreover studied concentrations of BAC had even slightly decreased the level of spontaneous mutagenesis. That is under the treatment with extracts of overground parts of elecampane in concentrations 50.0 and 100.0 mg/l the frequency of aberrant cells was 1.35% and 1.32% correspondingly that is in 1.24 beneath the control level, however this difference is not significant statistically. Similarly were the results of treatment with extracts of underground parts of elecampane. The obtained results thus are the additional evidence of the absence of mutagenic activity of studied extracts of elecampane. For the positive control the methyl methanesulfonate (MMS), widely used in experiments alkylating agent of direct action was chosen as representing well documented mutagenic activity in sort-time standard tests both *in vivo* and *in vitro* (Khudolei, 1999: 374–375; Natarajan, 2005: 312-317). Methyl methanesulfonate high frequently induced structural mutations in root meristem of barley. The level of aberrant cells was 6.56%, that is statistically exceeds the control level in 3.9 times ($p<0.01$). The number of chromosomal rearrangements per 100 metaphases was 7.43 that in 4.45 higher than in control ($p<0.001$) and is determined by the presence of more than one (2-3) chromosomal aberration in a single cell.

Table – The frequency and spectrum of chromosomal aberrations induced in barley seeds treated with Inula britannica extracts and methyl methanesulfonate

Variants	1. cells studied, total	1. frequency of aberrant cells (M ± m%)	Number of chromosomal aberrations per 100 metaphase cell		
			1. aberrations, total	2. chromosomal type	3. chromatid type
Water (negative control)	540	1.67 ± 0.55	1.67 ± 0.55	0.74 ± 0.37	0.93 ± 0.41
MMS, 5.0 mg/l (positive control)	579	6.56 ± 1.03***	7.43 ± 1.09***	3.11± 0.72**	4.32 ± 0.84***
I. britannica, extract of underground part					
BAC, 50.0 mg/l	520	1.35 ± 0.51	1.35 ± 0.51	0.77 ± 0.38	0.58 ± 0.33
BAC + MMS	570	2.81 ± 0.69••	2.98 ± 0.71••	1.23 ± 0.46•	1.75 ± 0.55•
MMS + BAC	535	3.36 ± 0.78•	3.55 ± 0.80•	2.06 ± 0.61	1.50 ± 0.53••
BAC, 100.0 mg/l	530	1.32 ± 0.50	1.32 ± 0.50	0.75 ± 0.37	0.57 ± 0.33
BAC + MMS	510	2.35 ± 0.67••	2.75 ± 0.72••	1.57 ± 0.55	1.18 ± 0.48••
MMS + BAC	525	2.86 ± 0.73••	3.05 ± 0.75••	1.71 ± 0.57	1.33 ± 0.50••
I. britannica, extract of aboveground part					
BAC, 50.0 mg/l	550	1.45 ± 0.51	1.45 ± 0.51	0.91 ± 0.40	0.55 ± 0.32
BAC + MMS	580	3.45 ± 0.76•	3.62 ± 0.78••	1.72 ± 0.54	1.90 ± 0.57•
MMS + BAC	580	3.62 ± 0.78•	3.62 ± 0.78••	1.90 ± 0.57	1.72 ± 0.54•
BAC, 100.0 mg/l	560	1.43 ± 0.50	1.43 ± 0.50	0.89 ± 0.40	0.54 ± 0.31
BAC + MMS	520	2.69 ± 0.71••	3.08 ± 0.76••	1.54 ± 0.54	1.54 ± 0.54•
MMS + BAC	540	3.15 ± 0.75•	3.33 ± 0.77••	1.85 ± 0.58	1.48 ± 0.52•

Note - * - $p<0.05$; ** - $p<0.01$; *** - $p< 0.001$ as compared to the control group;
• - $p<0.05$; •• - $p<0.01$ as compared to methyl methanesulfonate

The spectrum of chromosomal aberrations induced by MMS was wide and represented in all variants by rearrangements of both chromosomal and chromatid types. As well the high frequency was recorded for the anaphases with chromosomes separation and movement to the cell poles. It is known that fragmentation and pulverization of chromosomes occur under the mutagen exposure. The fragments may be single, pared or multiple. Those that lack centromeres do not participate in metakinesis and consequently do not move toward the mitotic poles in anaphase. The massive chromosomes fragmentation (pulverization) is characterized by chromosomes chaotic spreading in cytoplasm and ceases its participation in metakinesis. As the result the part of chromosome fragments may be included in daughter nucleus or resorbed or form separate micronucleus. The separate fragment may also reunite by their ends, such a reunions are stochastic and lead to the chromosomal aberrations (Kovalova, 2013: 33-41).

The concurrent exposure of barley seeds to MMS and plant extracts leads to alteration of genotoxic effect of MMS, the extent of those depends on the consistency of seeds treatment (table). That is, preliminary treatment of seeds with BAC of underground plant part in concentration 50.0 mg/l statistically reduces the frequency of MMS induced chromosomal aberrations (in 2.3 times; $p<0.01$). At the same time the number of structural mutations per 100 metaphases decreased by 2.5 times ($p<0.01$). The reverse combination of seeds treatment (MMS+BAC) also leads to statistically significant decrease of the level of induced mutagenesis. The general frequency of aberrant cells decreased by 1.95 times ($p<0.05$), and the number of chromosomal aberrations per 100 metaphases reduced in 2.1 times ($p<0.05$). The decrease of this indices at BAC+MMS variant takes place due to rearrangements of both chromosomal ($p<0.05$) and chromatid ($p<0.05$) types. The reverse combination of seeds treatment was characterized

by the significant decrease of structural chromatid rearrangements only ($p<0.01$). Similar results were obtained when using plant extracts in concentration 100.0 mg/l, but the alteration of mutagenic effect of MMS towards decrease was more pronounced. The frequency of aberrant cells and the number of chromosomal aberration per 100 metaphase statistically decrease by 2.8 ($p<0.01$) and 2.7 times ($p<0.01$) correspondingly when testing the variant BAC+MMS. The BAC treatment following MMS exposure also reduces this indices in 2.3 ($p<0.01$) and 2.4 ($p<0.01$) times, correspondingly. In both variants decrease was due to structural mutations of chromatid type ($p<0.01$). The preliminary BAC treatment decreases the frequency of chromatid aberrations by 3.7 times ($p<0.01$) and those following exposure - by 3.2 ($p<0.01$) times. It was established, based on comparative analysis no statistically significant differencies in the level of MMS induced mutagenesis upon pre- or post-exposure BAC treatment. The extracts of aboveground parts of *I. britannica* as well had been shown the ability to reduce the mutagenic effect of methyl methanesulfonate. Extracts pre-treatment in concentration 50.0 mg/l causes the lowering of the frequency of aberrant cells in 1.9 ($p<0.05$) and the number of structural rearrangements per 100 metaphases in 2.1 ($p<0.01$) times. The BAC treatment following exposure reduces mutagenic effect of MMS as well – the frequency of aberrant cells decreases in 1.8 ($p<0.05$) and the number of structural rearrangements in 2.1 ($p<0.01$) times and those reducing is mainly due to rearrangements of chromatid type. In the variant BAC+MMS the frequency of chromatid aberrations decrease by 2.8 time ($p<0.05$) and in reverse variant - by 2.9 ($p<0.05$) time.

Comparative analysis had reveled no statistically significant differencies in the level of MMS induced mutagenesis in concentrations 50.0 mg/l and 100.0 mg/l, also there was no differencies in the activity of extracts of underground or aboveground parts of *I. britannica.*

Thus the extracts of *I. britannica* have significant antimutagenic activity against MMS in all concentrations used and upon all variants of treatment. The maximum of activity was observed during BAC treatment preliminary MMS exposure and was 62.99% and 58.55% for the underground or aboveground parts, correspondingly (figure).

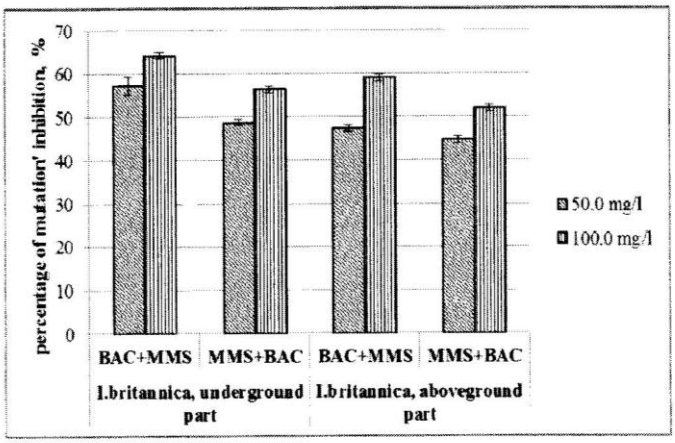

Figure – The percentage of mutation' inhibition (antimutagenic activity against MMS) of BAC from underground or aboveground parts of I.britannica

The MMS that is considered to be classic mutagen ($C_2H_6O_3S$) was selected to be positive control. This is monofunctional alkylating agent of direct action transferring only on CH_3-group. MMS leads to alkylation of purine bases and that to transitions and represents mutagenic activity in standard short-time tests *in vivo* и *in vitro,* induces SOS-response in umu-test on *Salmonella typhimurium* TA1535/pSK1002 and point mutations in bacteria without metabolic activation. In Drosophila MMS causes recessive somatic mutations and sex-linked lethal mutations. It was also shown the increase in the frequency of sister chromatid exchange and chromosomal aberrations, as well as neoplastic transformation in rodents cell culture. *In vivo* methyl methanesulfonate causes mutations in mice gametes and DNA damage, sister chromatid exchanges, chromosomal aberrations in somatic cells of rodents. In human cell culture MMS induces one-chain breaks and unplanned DNA synthesis, gene mutations, micronuclei and sister chro-

matid exchanges . MMS also represents toxic and mutagenic activity in various plant test-systems inducing chromosomal changes in root meristem of *Hordeum vulgare, Vicia faba, Arabidopsis thaliana.* MMS represents extraordinary wide spectrum of genetic activity in various test-systems which defines its choice as positive control in current experimental research (Khudolei, 1999: 374–375; Natarajan, 2005: 312-317).

Recently it was shown, that preliminary administration of various vitamin complexes to rats exposed to chemical mutagens leads to reduced DNA susceptibility to chemical impact . The thesis that preliminary induction of metabolic enzymes *in vivo* leads to weakening of effects of direct mutagens was theoretically grounded and experimentally confirmed by Sycheva L.P. and Zhurkov V.S. (Sycheva, 2003: 87-91).

It may be considered that antimutagenic effect of *I.britannica* extracts containing the complex of biologically active compounds is determined whether by activation or recovery of reparatory systems in a cell damaged by mutagen. Besides the ability of BAC to inhibit free radical processes induced by MMS and to stimulate chromosome reparation as well participates in antimutagenic activity of *I.britannica* extracts

Conclusion

The herbal extracts are considered to be the most of perspective preparations directing for leveling effects of mutagens. Antimutagenic effect of plant preparations is due to the high content of such a compounds as vitamins, pigments, aminoacids, phenols and polyphenols majority of whish possess antimutagenic activity (Al-Jaber, 2011: 293–307; Rice-Evans, 2001: 797–807; Havsteen, 2002: 67–202; Lin, 2008: 634–646; Middleton, 2000: 673–751; Lotito, 2000: 151–157; Hernes, 2001: 3109–3122; Milner, 2001; 1027–1031; Sprygin, 2006: 81-90; Miller, 2000: 312S–319S; Ajith, 2008: 24-28; Manjula, 2006: 113-116; Farghalaly, 2009: 1-7; Sram, 2012: 39– 49; Santos-Cervantes, 2007: 71-77). All classes of biologically active compounds are represented in extracts of *Inula britannica.*

Cytogenetic researches had revealed that extracts of underground and aboveground parts of *Inula* in concentrations 50.0 and 100.0 mg/l did not show any mutagenic activity and moreover reduced the level of spontaneous mutagenesis in root meristem of barley. When combined with MMS independently of the treatment sequence the plant extracts significantly reduced MMS induced mutagenesis. The obtained results demonstrate the presence of antimutagenic effect of studied extracts. There was revealed no significant difference in gene protective activity whether of aboveground or underground parts of *Inula* despite the latter contains more BAC.

It is well known that reparation of DNA damages is enzymatic process depending on the level of cell metabolism. It may be supposed that the BAC complex in Inula extracts intensifies the enzymatic reparation of DNA in a cell decreasing thus the level of MMS induced mutagenesis. The results of current research focused on the investigation of BAC of *I.britannica* extracts in modulation of cytogenetic activity of methyl methanesulfonate in plant test system may be extrapolated so that to presume their antimutagenic activity in mammals. The researches directed to confirm this presumption are initiated.

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МАЗМҰНЫ–СОДЕРЖАНИЕ

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