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Lovinskaya A.V.*, Kolumbayeva S.Zh., Esim Zh.I., Voronova N.

Al-Farabi Kazakh National University,
Kazakhstan, Almaty, *e-mail: annalovinska@rambler.ru

THE ANTIMUTAGENIC POTENTIAL OF EXTRACTS FROM *LIMONIUM GMELINII* FAMILY *PLUMBAGINACEAE* (= *LIMONIACEAE* LINCZ.)

The cytogenetic and mutagen-modifying activity of a complex of biologically active substances in extracts from shoot and root parts of Limonium gmelinii were investigated testing on count chromosome abnormalities of cells of barley root meristem. Plant extracts in concentrations 50.0 and 100.0 mg/L have no mutagenic activity, but, on the contrary, reduced the level of spontaneous mutagenesis. As a result of the combined effect of methanesulfonate mutagen (MMS) and plant extracts, a statistically significant decrease in the level of MMS-induced mutagenesis was observed. Extracts of BAS from the shoot and root parts of L. gmelinii in all concentrations and all variant of treatment have strong antimutagenic activity against MMS. The maximum antimutagenic effects were observed during BAS preliminary treatment MMS exposure and were 64.70% and 67.46% for the root and shoot parts, correspondingly. The mitotic index (MI) of the root meristem of germinating seeds, separately and jointly treated with MMS and extracts, was studied. Plant extracts gave a mitostimulatory effect, while MMS significantly reduced the proliferative activity of the root meristematic cells as compared to the control. Pre- and post- treatment of BAS from the shoot and root parts statistically significantly increased the mitotic activity of the root meristem in comparison with MMS. Genoprotective action of these BASs can be due to their ability to inhibit free radical processes, enhanced by the action of various genotoxicants, and to stimulate chromosome repair. Herbal preparations can be considered the most promising as therapeutic agents aimed at leveling the action of mutagens on the body.

Key words: Limonium gmelinii, biologically active substances, antimutagen, chromosome aberrations, mitotic index.

Ловинская А.В.*, Колумбаева С.Ж., Есім Ж.И., Воронова Н.

Әл-Фараби атындағы Қазақ ұлттық университеті,
Қазақстан, Алматы қ., *e-mail: annalovinska@rambler.ru

Plumbaginaceae (= Limoniaceae Lincz.) тұқымдасындағы *Limonium gmelinii* өсімдіктер сығындыларының антимутагендік потенциалы

Арпа тұқымының тамырының ұрық меристемасының клеткаларындағы хромосомалық аберрацияларды есепке алу тесті қолдану негізінде Limonium gmelinii өсімдіктің жер асты және жер үсті мүшелерінің сығындыларының биологиялық белсенді заттар (ББЗ) кешенінің цитогенетикалық және мутагенді өзгермелік белсенділігі зерттелді. 50,0 және 100,0 мг/л концентрациясы бар өсімдік сығындылар мутагендік белсенділік көрсеткен жоқ, бірақ, керісінше, спонтанды мутагеннің деңгейін төмендетті. Стандартты метилметансульфонат (ММС) мутагеннің және өсімдіктер сығындыларының қосымша әсері болғанда индукцияланған ММС мутагенездің деңгейі статистикалық сенімді ретінде төмен болғаны анықталды. ММС-қа қарсы жоғары деңгейде Гмелин кермегінің жер асты және жер үсті мүшелерінің ББЗ сығындылары антимутагенді белсенділігін көрсетті. ББЗ-ның максималды антимутагенді тиімділігі тұқымдарды алдын ала, сосын барып ММС-пен өңдегенде байқалды, яғни 64,70% (жер асты мүшесі) және 67,46% (жер үсті мүшесі) аралығында. ММС-пен және сығындылармен бөлек және қосымша өңдеген жағдайда тұқым өсінділердің тамыр меристемасының митоздық индексі (МИ) зерттелді. Өсімдік сығындылар митозды ынталандыру нәтижесін көрсетті. ММС тамыр аймағындағы меристемалық

клеткалар популяциясының пролиферативті белсенділігін бақылаумен салыстырғанда статистикалық сенімді ретінде төмендетті. Тұқымдарды өсімдіктердің жер асты және жер үсті мүшелерінің ББЗ-мен алдын ала және кейінгі түрде өңдегенде тамыр меристемасының митоздық белсенділігінің деңгейі ММС-пен салыстырғанда статистикалық сенімді ретінде жоғарылады. ББЗ-ның генопротекторлық әсері олардың әртүрлі генотоксиканттардың әсерінде ұлғая түскен босрадикалды процестерді тежеуге қабілетті болу мүмкін және хромосомалардың репарациясын ынталандырады. Өсімдік препараттарды ем беретін құралдар, яғни мутагендердің организмге әсерін жоюға бағытталған ретінде санауға болады.

Түйін сөздер: гмелин кермегі, биологиялық белсенді заттар, антимутаген, хромосомалық аберрациялар, митоздық индекс.

Ловинская А.В.*, Колумбаева С.Ж., Есим Ж.И., Воронова Н.

Казахский национальный университет имени аль-Фараби,
Казахстан, Алматы, *e-mail: annalovinska@rambler.ru

Антимутагенный потенциал экстрактов растений *Limonium gmelinii* семейства *Plumbaginaceae (= Limoniaceae Lincz.)*

Изучена цитогенетическая и мутагенмодифицирующая активность комплекса биологически активных веществ в экстрактах подземной и надземной частей растений Limonium gmelinii с использованием теста по учету хромосомных аберраций в клетках корневой зародышевой меристемы семян ячменя. Растительные экстракты в концентрациях 50,0 и 100,0 мг/л не проявили мутагенной активности, а, наоборот, несколько снизили уровень спонтанного мутагенеза. В результате комбинированного воздействия стандартного мутагена метилметансульфоната (ММС) и растительных экстрактов наблюдалось статистически значимое снижение уровня индуцированного ММС мутагенеза. Экстракты БАВ из подземной и надземной частей кермека Гмелина при всех концентрациях и вариантах обработки проявили сильную антимутагенную активность против ММС. Максимальные антимутагенные эффекты БАВ выявлены при предварительной обработке семян экстрактами с последующим воздействием ММС, составившие 64,70% (подземная часть) и 67,46% (надземная часть). Изучен митотический индекс (МИ) корневой меристемы прорастающих семян, раздельно и совместно обработанных ММС и экстрактами. Растительные экстракты дали митозстимулирующий эффект, в то время как ММС статистически значимо снижал пролиферативную активность популяции меристематических клеток в корневой зоне по сравнению с контролем. Предварительная и последующая обработки семян БАВ из подземной и надземной частей растений статистически значимо увеличили митотическую активность корневой меристемы по сравнению с ММС. Генопротекторное действие данных БАВ может быть обусловлено их способностью ингибировать свободнорадикальные процессы, усиленные воздействием различных генотоксикантов, и стимулировать репарацию хромосом. Растительные препараты можно считать наиболее перспективными в качестве лечебных средств, направленных на нивелирование действия мутагенов на организм.

Ключевые слова: кермек Гмелина, биологически активные вещества, антимутаген, хромосомные аберрации, митотический индекс.

Introduction

The ecological crisis, caused by the environmental pollution resulting from human activity, is typical for most regions of our planet. The accumulation of different xenobiotics in the biosphere leads to an increase in the incidence of the population, a decrease in the number of rare and endemic species of plants and animals, as well as the destabilization of natural ecosystems (Artyukhov, 2006: 208-215; Kurlyandskii, 2002: 385-406). Most pollutants have a toxic and mutagenic potential, which is manifested in the body directly by interacting with DNA molecules or indirectly as a result of activation of the processes of intracellular free radical formation and inhibition of DNA repair system activity (Holland, 2002: 165-178; Natarajan, 2006: 375-381). Under conditions of negative internal and external factors, the system of maintaining DNA equilibrium can degrade and genome instability and an increase in DNA adduct level (Vasil'eva, 2009: 753-757; Xia, 2008: 464-473). It is almost impossible to exclude human contact with toxic and mutagenic factors in the current situation. Therefore, it is of great importance to search for protectors of natural origin from their impact. Identifying new antimutagens, studying the mechanism of their action, practical ways of applying them to reduce professional, general and age-related risks to people and preserving biodiversity is one

of the most urgent tasks (Goncharova, 2005: 19-32; Zasukhina,2008: 464-473). Antimutagenic properties have many biologically active substances (BAS) of natural origin, including vitamins, plant flavonols, phytohormones, polypeptides, amino acids, etc. Most of them are antioxidants and can increase the body's resistance to the mutagenic and toxic effects of a wide range of pollutants. The aim of the current study was to research antimutagenic potential of extracts from the medicinal plant *Limonium gmelinii* (fam. *Plumbaginaceae*) growing in Kazakhstan.

Materials and methods

The object of the study was the seeds of spring barley (*Hordeum vulgare* L.) Baisheshek variety attributed to Almaty region. The wide use of barley seeds for cytogenetic studies is due primarily to a small number of chromosomes (7 pairs, 2n = 14) and large sizes (6-8 μm). The barley has a low frequency of spontaneous mutation and, at the same time, a sufficiently high sensitivity to external damaging effects. Thus, it is a unique test object for indicating the biological action of xenobiotics (Geras'kin, 201: 55-56). As the standard mutagen was used methyl methanesulfonate (MMS, $C_2H_6O_3S$). It is an alkylating agent of direct action, which has activity in standard short-term tests *in vivo* and *in vitro*. The validity of the choice of MMS as a positive control is due to an extremely wide spectrum of genetic activity in different test systems (Khudolei, 1999: 374-375). Extracts from the shoot and root parts of *Limonium gmelinii* (Willd.) Kuntze (family *Plumbaginaceae*) containing a complex of biologically active substances was used as subjects for phytotoxicity, mutagenic and antimutagenic activity.

Aqueous solutions of MMS were used in a concentration of 5.0 mg/L, and aqueous solutions of plant extracts were used in concentrations 50.0 and 100 mg/L. The seeds were treated to separate and consecutive with a mutagen and extracts for 4 hours. After each treatment, the seeds were washed, lightly dried and germinated in Petri dishes on filter paper wetted with distilled water at 25±1°C in the incubator.

Mutagenic / antimutagenic activity of the plant extracts was determined using chromosome aberration test. The cytogenetic test informs about the frequency and types of structural rearrangements (aberrations) of chromosomes and about changes in their number. The meristematic root tip tissue was used to study somatic chromosomes at the stage of mitosis and to account for chromosome rearrangements (Nemtseva, 1970: 84-122). The mitotic index (the ratio of dividing cells to the total number of cells) was determined to study the mitotic activity of the root germinal meristem. Statistical processing of the data was carried out in the add-in «Analysis ToolPak» of Microsoft Excel. The mean and standard errors were calculated. The reliability of the differences in the mean was estimated by the Student's test. Differences were considered reliable with a confidence level of 0.95.

Results and discussion

The results of a cytogenetic study of barley seeds jointly treated with mutagen and BAS extracts from *L.gmelinii* are presented in Table 1. The spontaneous mutation level in the root embryonic meristem of barley seeds treated with distilled water was 1.57%. MMS in concentration 5.0 mg/L induced structural rearrangements in chromosome in 4.4 times ($p<0.001$) higher than the control level. The seed's treatment of BASs from *L.gmelinii* before germination reduced the frequency of aberrant cells and number of chromosomal aberrations per 100 metaphases in comparison with the control variant.

When combined with the effects of plant extracts and mutagen in different treatment combinations, a significant modification of the level of MMS-induced mutagenesis in the direction of its reduction was observed. Thus, pretreatment with an extract from root part of *L.gmelinii* in a concentration 50.0 mg/L followed by treatment with MMS resulted in the frequency of aberrant cells statistically significantly decreased in 2.5 times ($p<0.01$) and the number of chromosomal aberrations per 100 metaphase reduced in 2.7 times ($p<0.01$) in comparison with MMS treatment. At the same time, the frequency of rearrangements of both chromosomal and chromatid types decreased. The level of structural mutations of the chromosome type decreased by 2.1 times ($p <0.05$), and the chromatid type reduced by 4.3 times ($p <0.01$), which corresponds to the control level.

In the variant with the reverse sequence of seed treatment with genotoxicant and plant extract (MMS+BAS), the level of MMC-induced mutagenesis statistically significantly decreased at the same concentration. The frequency of aberrant cells decreased by 2.2 times ($p <0.01$), and the number of chromosomal aberrations per 100 metaphase decreased by 2.4 times ($p <0.01$). A significant decrease in these indices was equally due to rearrangements of the chromosome (2-fold, $p <0.05$) and chromatid (4.9 times, $p <0.05$) types.

Table 1 – The frequency and spectrum of chromosomal aberrations induced in barley seeds treated with L. gmelinii extracts and methyl methanesulfonate

Variants	cells studied, total	frequency of aberrant cells (M ± m, %)	Number of chromosomal aberrations per 100 metaphase cells		
			aberrations, total	chromosomal type	chromatd type
Water (negative control)	510	1.57 ± 0.55	1.57 ± 0.55	0.98 ± 0.44	0.59 ± 0.34
MMS, 5.0 mg/L	540	6.85±1.09***	7.96 ± 1.16***	4.26±0.87***	3.70 ± 0.81**
L. gmelinii, extract of root part					
BAS, 50.0 mg/L	550	1.27 ± 0.48	1.27 ± 0.48	0.73 ± 0.36	0.55 ± 0.32
BAS+MMS	575	2.78 ± 0.69••	2.96 ± 0.71••	2.09 ± 0.60•	0.87 ± 0.39••
MMS+BAS	580	3.10 ± 0.72••	3.28 ± 0.74••	2.07 ± 0.59•	1.21 ± 0.45•
BAS, 100.0 mg/L	550	1.09 ± 0.44	1.09 ± 0.44	0.73 ± 0.36	0.36 ± 0.26
BAS+MMS	570	2.46 ± 0.65••	2.81 ± 0.69•••	1.75 ± 0.55•	1.05 ± 0.43••
MMS+BAS	550	3.09 ± 0.74••	3.27 ± 0.75••	2.00 ± 0.60•	1.27 ± 0.48•
L. gmelinii, extract of shoot part					
BAS, 50.0 mg/L	590	1.36 ± 0.48	1.36 ± 0.48	0.68 ± 0.34	0.68 ± 0.34
BAS+MMS	580	2.24 ± 0.61••	2.59±0.66•••	1.55 ± 0.51•	1.03 ± 0.42••
MMS+BAS	585	2.56 ± 0.65••	3.08 ± 0.71••	2.05 ± 0.59•	1.03 ± 0.42••
BAS, 100.0 mg/L	575	1.22 ± 0.45	1.22 ± 0.45	0.70 ± 0.34	0.51 ± 0.29
BAS+MMS	580	2.59 ± 0.66••	2.76 ± 0.68••	1.90 ± 0.57•	0.86 ± 0.38 ••
MMS+BAS	560	3.04 ± 0.73••	3.39 ± 0.76••	2.14 ± 0.61	1.25 ± 0.47•

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

A similar picture was revealed when using *L.gmelinii* extracts from the root part in a concentration 100.0 mg/L. Thus, seed pre-treatment of BAS reduced the frequency of aberrant cells and the number of chromosomal aberrations per 100 metaphases by 2.8 times (p <0.01). Post-mutagen treatment of BAS was also reduced these indicators by 2.2 (p<0.05) and 2.4 (p<0.01) times, respectively. In both variants, there was a statistically significant decreased in the structural mutations of the chromosomal and chromatid types. With the pre-treatment of BAS, the frequency of chromosome-type disorders decreased by 2.4 times (p<0.05), and the chromatid type is 3.5 times (p <0.01). With post-exposure to BAS (after the mutagen), the frequency of aberrations of the chromosome type decreased by 2.1 (p <0.05), and the chromatid type reduced by 2.9 times (p <0.05). A comparative analysis of the effectiveness of the sequence of application of BAS pre- or post-treatment with mutagen did not reveal statistically significant differences in the reduction level of MMS-induced mutagenesis.

Modification of the mutagenic effect of methyl methanesulfonate towards its reduction was also observed when seed treatment from the shoot part of *L.gmelinii* extracts. Pre-treatment of seeds with extracts in a concentration 50.0 mg/L led to a decrease in the frequency of metaphases with chromosomal aberrations and the number of structural rearrangements in chromosomes per 100 cells in 3.1 times (p <0.01). Post-mutagen treatment also contributed to a decrease in the mutagenic effect of MMS. The frequency of aberrant cells and the number of structural mutations were lower in 2.7 (p <0.01) and 2.6 (p <0.01) times as compared with MMS, respectively. In the spectrum of structural mutations, a significant decrease in chromosome and chromatid rearrangements was observed in 2.7 (p <0.05) and 3.6 (p <0.01) times in pre-treatment and 2.1-fond (p <0.05) and 3,6-fond (p <0,01), respectively, with post-treatment of BAS seeds.

Plant extracts from the shoot part of *L.gmelinii* in a concentration 100 mg/L also reduced the level of MMS-induced mutagenesis irrespective of the treatment sequence. Thus, in the variant of BAS+MMS, the frequency of aberrant cells and the number of structural rearrangements in chromosomes per 100 metaphases decreased by 2.6 (p<0.01) and 2.9

(p<0.01) times, respectively, compared with MMS. With the reverse sequence of MMS+BAS, these indicators decreased by 2.3 (p <0.01) and 2.4 (p <0.01) times, respectively, compared to MMS. The decrease in the level of MMS-induced mutagenesis was due to both types of rearrangements, with the exception of the MMS+BAS variant, where a significant reduction was observed only due to chromatid rearrangements. In the variant of BAS+MMS, the frequency of chromosomal and chromatid rearrangements significantly decreased by 2.2 (p <0.05) and 3.2 (p <0.01) times, respectively, and by an inverse processing sequence reduced by 2.0 times (statistically not significant) and 3.0 (p <0.05) times.

Comparative analysis of the level of modification of the MMS-induced mutagenic effect with the *L.gmelinii* extract did not reveal significant differences in the frequency of aberrant cells and the number of structural rearrangements in chromosomes per 100 cells using concentrations 50.0 and 100.0 mg/L. There were no statistically significant differences in the decrease of these parameters when using *L.gmelinii* extracts from the shoot and root parts.

Extracts of BAS from shoot and root parts of *L.gmelinii* have strong antimutagenic activity against MMS in all concentrations used and upon all variants of treatment. The maximum antimutagenic effects were observed during BAS preliminary treatment MMS exposure and were 64.70% and 67.46% for the root and shoot parts, correspondingly (figure).

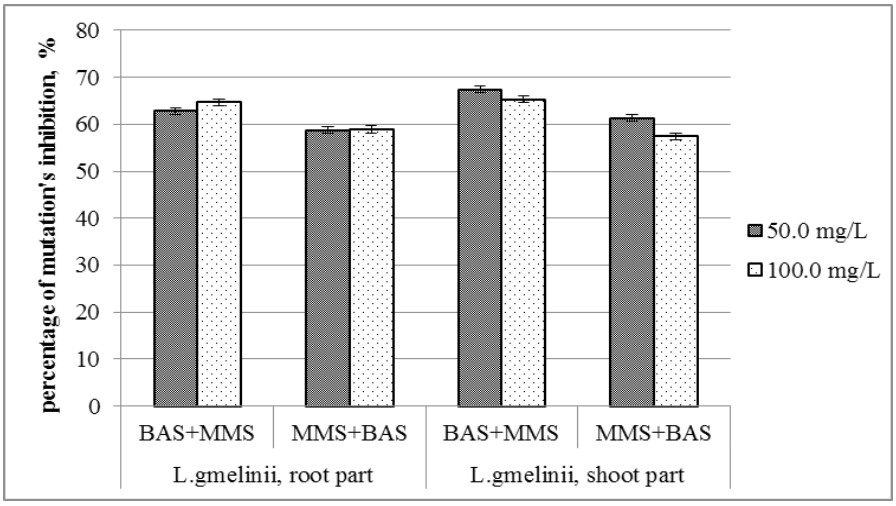

Figure – Percentage of mutation's inhibition (antimutagenic activity) of BAS extracts from the shoot and root parts of L.gmelinii against MMS

The mitotic index (MI) is used to evaluate the proliferative activity of tissues, and also as one of the tests in the analysis of mutagens. The mitotic index informs about the normal, depressed or intensified mitotic activity of the tissue. This indicator can be used in assessing the toxicity, mutagenicity and antimutagenic potential of different agents.

We studied the MI of the root meristem of germinating seeds, separately and jointly treated with MMS (positive control) and extracts from the shoot and root parts of *L.gmelinii* in concentrations 50.0 and 100.0 mg/L (Table 2).

The mitotic index in the root meristem of seeds soaked and germinated on distilled water was 6.94% (negative control). This indicator decreased by 2.7 times (p <0.01) in the treatment of MMS. It indicates that the mutagen suppresses the proliferative activity of the cell population.

The MI in the root meristem of seeds soaked and germinated on aqueous solutions of BAS from the root part of *L. gmelinii* in a concentration 50.0 mg/L was 9.67%, and in a concentration 100.0 mg/L was 11.63%. The MI statistically significantly increased in 1.4 (p<0.05) and 1.8 (p<0.01) times when treatment of seeds with the BAS complex, respectively, in concentrations 50.0 mg/L and 100.0 mg/L compared with the negative control (water). It indicates about the stimulating effect of BAS on the proliferative activity of the root meristem.

Table 2 – Mitotic index of the root meristem of germinating barley seeds treated with methyl methanesulfonate and biologically active substances from L. gmelinii

Variant	Mitotic index (%)	
	50.0 mg/L	100.0 mg/L
BAS from *L. gmelinii* (root part)	9.67 ± 0.51•	11.63 ± 1.03•
BAS + MMS	5.66 ± 0.67**	6.07 ± 0.67**
MMS + BAS	4.87 ± 0.55**	5.66 ± 0.96**
BAS from *L. gmelinii* (shoot part)	8.81 ± 0.55	9.82 ±0.55••
BAS + MMS	4.47 ± 0.62*	5.03 ± 0.73**
MMS + BAS	4.37 ± 0.60*	4.98 ± 0.61**
Distilled water (negative control)	6.94 ± 0.80	
MMS, 5.0 mg/L (positive control)	2.57 ± 0.38••	
Note – *-p<0.05; **-p<0.01 as compared to methyl methanesulfonate; •⁻p<0.01; •⁻p<0.001 as compared to the negative control (water)		

The proliferating activity of the root meristem cell population was statistically significantly increased by the joint treatment of seeds with BASs and MMS as compared to the treatment with the mutagen. However, the degree of increase in the MI depended on the sequence of MMS and BAS treatment. Thus, the pre-treatment of barley in a solution of BASs in concentrations 50.0 and 100.0 mg/L, followed by soaking in a solution of MMS, statistically significantly increased the MI in 2.2 (p <0, 01) and 2.4 (p <0.01) times, respectively, compared to soaking only in the mutagen solution. Post-MMS-treatment of seeds with BASs in these same concentrations also increased the mitotic activity of the cells compared to treatment with MMS. At the same time, BASs in a concentration 50.0 mg/L statistically significantly increased the MI in 1.9 (p <0.01) times, and BASs in a concentration 100.0 mg/L in 2.2 (p<0.01) times.

Extracts from the shoot part of *L.gmelinii* also increased the proliferative activity of the primary root meristematic cells of the barley seeds. The MI in the variant with seed treatment of BAS was statistically significantly increased by 1.4 times (p <0.01) only with a concentration 100 mg/L in comparison with the negative control (water). In the variant of seed treatment of BAS+MMS, statistically significant increase in the proliferative activity of cells inhibited by MMS was observed. The mitotic index increased in comparison with the treatment of only MMS in 1.7 (p<0.05) and 2.0 (p <0.01) times in concentrations 50.0 and 100.0 mg/L, respectively. With the reverse sequence of seed treatment, there was also an increase in the proliferation of the cell population. At the same time, the MI values increased in 1,6 (p <0,05) and 1,9 (p <0,01) times in concentrations 50,0 and 100,0 mg/L. Comparative analysis of the MI showed that pre- and post-treatment of seeds with BASs from root and shoot parts of *L.gmelinii* statistically significantly decreased the inhibitory effect of proliferative activity of MMS.

Thus, cytogenetic studies have shown that extracts from *L.gmelinii* in the concentrations used have not mutagenic activity, but, on the contrary, even slightly reduced the level of spontaneous mutagenesis in the root meristem of barley. As a result of combined action of MMS and plant extracts, regardless of the treatment sequence, a statistically significant decrease in the frequency of aberrant cells and chromosomal aberrations per 100 metaphase was observed. It indicates the presence of antimutagenic activity in the extracts. There were no significant differences in the antimutagenic activity of extracts from the shoot and root parts of *L.gmelinii*, despite the greater content of BAS in the root part of plants. Plant extracts showed a mitostimulatory effect, while MMS statistically significantly reduced the proliferative activity of root meristematic cells compared to the control (water). Pre- and post- treatment of BAS seeds in all concentrations statistically significantly increased the mitotic activity of the root meristem in comparison with MMS.

It is known that DNA repair is an enzymatic process, depending on the level of cellular metabolism. It is shown that the preliminary administration of various vitamin complexes to rats exposed to different chemical mutagens leads to decreased

DNA susceptibility to damaging effect. L.P. Sycheva and V.S. Zhurkov theoretically substantiated and experimentally confirmed the thesis that the preliminary induction of enzymatic metabolizing systems *in vivo* leads to a weakening of the effects of direct mutagens (Sycheva, 2003:87-91).

The antimutagenic effect of the extracts from *L.gmelinii* containing a complex of biologically active substances can be caused by the activation or restoration of the repair systems of a cell damaged by a mutagen. In addition, the genetic protective effect of these BASs may be due to their ability to inhibit free radical processes, enhanced by the action of different genotoxicants, and to stimulate chromosome repair. Herbal preparations can be considered the most promising as therapeutic agents aimed at leveling the action of mutagens on the body. Antimutagenic action of herbal preparations is associated with the content of such substances as vitamins, pigments, amino acids, phenols and polyphenols, most of which have antimutagenic activity (Ajith, 2011: 2676-2680; Al-Jaber, 2011: 293-307; Farghalaly, 2009: 1-7; Havsteen, 2002: 67-202; Hernes, 2001: 3109-3122; Kumar, 2014: 815-826; Lin, 2008: 634-646; Lotito, 2000: 151-157; Manjula, 2006: 113-116; Medvedeva, 2003: 27-29; Middleton, 2000: 673-751; Miller, 2000: 312S-319S; Milner, 2001: 1027-1031; Rice-Evans, 2001: 797-807; Saraç, 2014: 60-64; Sprygin, 2006: 81-90; Sram, 2012: 39-49; Strusovskaya, 2012: 128-131).

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