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БАЯНДАМАЛАРЫ

ДОКЛАДЫ

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
РЕСПУБЛИКИ КАЗАХСТАН

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STUDY OF ANTIGENOTOXIC POTENTIAL OF THE ROSEHIP (*ROSA MAJALIS* HERRM.) OF THE FAMILY *ROSACEAE*

Abstract. Increasing the body's resistance to various environmental pollutants' adverse effects is one of medicine's essential tasks. In this regard, an active search for antimutagens to eliminate or weaken mutagens' effect in the body is currently underway. One of the promising sources of antimutagenic compounds is the medicinal plant *Rosa majalis* Herrm (rosehips). The genotoxic and antigenotoxic activity of rosehips was studied on cells of bone marrow, spleen, liver, and kidneys of laboratory mice using an alkaline variant Comet assay. It was found that rosehip infusions in various concentrations (infusion, diluted infusion and herbal tea) do not have a genotoxic effect on the cells of the studied organs of laboratory animals. The medicinal rosehip's combined action with classical mutagen MMS significantly reduced ($p<0.01$) MMS-induced mutagenesis level. The various rosehip infusions used did not show statistically significant differences among themselves. The results obtained indicate the antigenotoxic activity of *R. majalis* infusions.

Keywords: rosehip, mutagen, genotoxicity, gene protector, Comet assay.

Introduction. Currently, the environment contains a critical content of chemical and physical mutagens. By 2021, about 15 thousand new compounds have been synthesized and produced, 15% of which are used in various human activity fields in the world [1]. Chemicals can cause various mutations in somatic and germ cells of the body [2]. The demand for new genetic monitoring methods to detect mutagenic and carcinogenic factors in the environment is due to the awareness of the threat to human health and species biodiversity. Mutagens can damage single nucleotides, nucleotide pairs and cause DNA strand breaks. Besides, mutagens enhance mutagenesis and are also directly related to the development of carcinogenesis [3].

Since the 1990s, interest in traditional therapies, including herbal medicine, has increased dramatically. About 40% of pharmaceutical products based on medicinal plant raw materials are produced in the world [4]. Biologically active substances in plants can have anti-inflammatory, antiarrhythmic, antioxidant, gastro- and hepatoprotective, hemorheological and other effects [1]. In connection with the urgency of mutagenesis and carcinogenesis, the question of creating synthetic dosage forms or the search and screening of antimutagens and anticarcinogens of plant origin [3].

Many scientific studies were carried out proving the antioxidant properties of biologically active substances in plants, which are recommended to prevent and treat benign and malignant tumors. It is known that free radicals and active oxygen metabolites in the body can react with proteins, nucleic acids, and lipids, causing changes in the genetic material and inactivation of enzymes. Therefore, human health depends on the effectiveness of antioxidant mechanisms [5, 6]. The harmful effects of peroxides and oxygen radicals on the body increase interest in natural antioxidants, especially polyphenols. Antioxidants are found in fruits, vegetables, grains, legumes, juices, wine, tea, and many herbs [7]. Herbaceous plants are a rich source of antioxidants, which are more active than fruits and vegetables [8].

There are about 6000 species of higher plants in Kazakhstan; 1406 are medicinal. Among them, only 230 species are used in official medicine in Kazakhstan. Among these plants that contain flavonoids and

their derivatives (60% of species), alkaloids (42%), vitamins (32%), tannins (29%), coumarins (25%), etc. [9, 10]. In the *Rosaceae* family, rosehip, cinquefoil, hawthorn, chokeberry, mountain ash, burnet, bird cherry, raspberry, blackberry, strawberry, stone berry, and other plants used as medicinal plants. One of the useful plants with significant raw material resources is the rosehip (*Rosa majalis*).

Rosehip (*Rosa majalis* Herrm) is a rich source of vitamin C and polyphenols. Rosehip extract can absorb reactive oxygen species (ROS). It is the leader in antioxidant activity among plants of the *Rosaceae* family [11, 12]. Fruits, which are high in antioxidants, have phytoncide and powerful bactericidal properties. The prevention and treatment of diseases associated with a lack of vitamins are used decoctions of rosehips, vitamin extracts, syrups, and tablets. Our study aimed to study the antimutagenic activity of rosehip infusions on organisms of laboratory mice connected with the above.

Materials and methods. Laboratory mice of the *BALB/c* line (*Mus musculus* Linn.) are the object of study in experiments to study the antimutagenic potential of infusions of the *Rosaceae* family (*Rosa majalis* Herrm). An infusion, a diluted 1/1 infusion, and herbal tea from the rosehip plant (*R. majalis*, family *Rosaceae*) were taken as the test substance. The direct-acting mutagen methyl methanesulfonate (MMS, $C_2H_6O_3S$) at a 40 mg/kg concentration was used as a positive control [13]. The infusion of *R. majalis* was prepared according to the standard recipe: 10 g (1 tbsp) of the fruit was placed in an enamel bowl, 200 ml (1 glass) of hot boiled water was poured, and heated in a water bath for 15 minutes, it was cooled for 45 min at room temperature, filtered, the remaining raw material was wrung out. The volume of the obtained infusion was brought to 200 ml with boiled water. A diluted 1/1 infusion was prepared from 200 ml of fruit infusion, which was prepared according to the above recipe, diluted with 200 ml of boiled and cooled water at room temperature. Herbal tea from the *R. majalis* plant was prepared as follows: 1 filter bag was poured with 200 ml of boiling water, cooled at room temperature.

In total, 40 laboratory mice of the *BALB/c* line (*Mus musculus* Linn.) Where used in the experiment in the fertile period (2-3 months) weighing an average of 25-30 g. The experiments were carried out on eight groups of laboratory mice, five individuals each: I - intact animals (negative control); II - animals that received the standard MMS mutagen intraperitoneally (positive control); III - animals that received oral rosehip infusion; IV - animals that received orally herbal rosehip tea; V - animals that received orally diluted 1/1 infusion of rosehip; VI - animals that received MMS intraperitoneally and orally with rosehip infusion; VII - animals that received MMS intraperitoneally and orally with rosehip herbal tea; VIII - animals that received intraperitoneal MMS and orally diluted rosehip infusion. The care of laboratory animals was carried out following international standards [14]. The substances were administered for five days daily. The animals were sacrificed with isoflurane anesthesia 24 hours after the last injection of the test substances, and the internal organs (bone marrow, liver, spleen, and kidneys) were removed.

Using the Comet assay [13, 15], the antimutagenic potential of the compounds under study was studied. The bone marrow, kidneys, liver, and spleen were examined using an alkaline variation of the Comet assay. The "DNA comets" analysis was carried out visually using an Olympus microscope (Japan) at 40x magnification. At least 500 "DNA comets" were analyzed in each variant of the experiment. “DNA comets” were ranked into five conditional types: class I: 0-6.0%, class II: 6.1-17%, class III: 17.1-35.0 %, class IV: 35.1-60.0%, class V: 60.1-100.0% DNA breaks) [16]. The index of DNA comet (IDC) was used to determine the degree of DNA damage and was calculated by the formula: $IDC = \frac{0n_1+1n_2+2n_3+3n_4+4n_5}{\sum n}$, where n_1-n_5 is the number of "DNA comets" of each class, Σn is the sum of the counted "DNA comets".

The damage index (DI) as an indicator of the genotoxic effect of the agent was calculated using the formula: $DI = \frac{IDC_e}{IDC_c}$, where IDC_e is IDC in the experimental group, IDC_c is IDC in the control group. If DI> 2, then the test substance has a pronounced genotoxic activity.

Statistical analysis of the obtained results was carried out using the StatPlus5Pro program (AnalystSoft Inc., version 6). For each experimental group, mean values and standard errors of the mean were determined. Differences were considered statistically significant at confidence levels of 95% and higher ($p<0.05$).

Results and discussion. The mutagenic and antimutagenic activity of the medicinal plant rosehip (*R. majalis*) in various concentrations on the organism of laboratory mice was studied. The table shows the analysis' results of DNA damage in the cells of various organs of mice subjected to joint and separate exposure to rosehip infusions and the standard MMS mutagen.

The degree of DNA damage in the cells of laboratory mice's internal organs under separate and combined effects of rosehip infusions and MMS

Variant	DNA comet index (IDC) in the cells of the internal organs of mice			
	bone marrow	spleen	liver	kidney
I group, control/intact	0.14±0.03**	0.17±0.04**	0.15±0.03**	0.17±0.06**
II group, MMS, 40 mg/kg	3.58±0.13	3.26±0.38	3.27±0.44	2.82±0.21
III group, infusion	0.26±0.09**	0.11±0.01**	0.20±0.06**	0.18±0.11**
IV group, herbal tea	0.12±0.02**	0.24±0.12**	0.30±0.07**	0.24±0.05**
V group, diluted infusion	0.11±0.01**	0.33±0.14**	0.29±0.03**	0.34±0.12**
VI group, infusion + MMS	0,66±0,34**	0.96±0.42*	0.83±0.52*	0.66±0.45*
VII group, herbal tea + MMS	0.31±0.20**	0.57±0.38*	0.64±0.37*	0.46±0.25**
VIII group, diluted infusion + MMS	0.57±0.21**	1.03±0.23*	0,64±0.47*	1.09±0.11**
Note: *p<0.01, ** p<0.001 compared to MMS (positive control)				

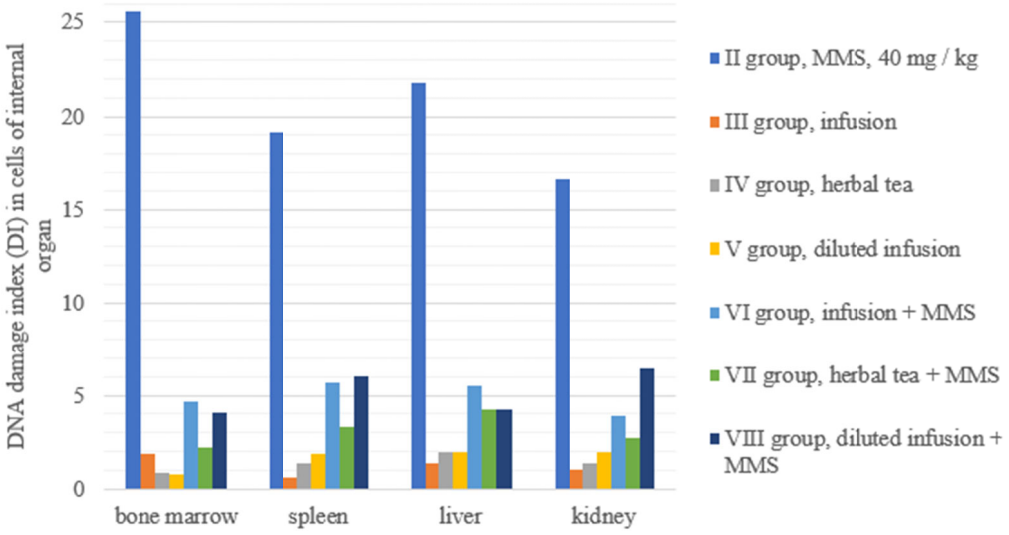
In the alkaline version, DNA comet analysis reveals single- and double-stranded DNA breaks, alkaline-labile sites, as well as apurinic and apyrimidinic sites arising as a result of the excisional repair. From the results presented in the table, the IDC value in the bone marrow cells exposed to MMS was statistically significantly ($p<0.001$) higher than in intact animals. The IDC value was at the negative control level in the bone marrow cells of animals exposed to rosehips' variants. Most DNA comets can be attributed to classes I (0-6% of DNA breaks). When exposed to rosehip infusion and MMS, the IDC values were statistically significantly lower compared with the positive control ($p <0.001$) – 5,4-fold (infusion+MMS), 6.3-fold (diluted infusion), 11.5-fold (herbal tea+MMS). Simultaneously, DNA comets of II and III damage classes were noted (6.1-35% of DNA breaks).

In spleen cells of mice exposed to rosehip infusions, the index of DNA comet was at the negative control level, and most DNA comets were mainly classified as class I (0-6% of DNA breaks). The IDC under the influence of MMS increased 19.2-fold ($p<0.001$) times compared to the negative control. IDCs with the combined action of rosehip infusions and MMS are statistically significantly lower than the positive control ($p<0.01$).

In MMS-treated mice's liver cells, the IDC value was statistically significantly higher by 21.8 times ($p<0.001$) than the negative control. When the rosehip infusion, diluted infusion, and herbal tea in liver cells were treated into mice, the IDC was at the level of negative control, and DNA comets I-II (0-17%) class were observed. The DNA comets observed in mice's liver cells taking MMS+infusion, MMS+diluted infusion, and MMS+herbal tea can be attributed to II-VI (17-60%) damage class. When combined with a mutagen in mice, rosehip modified its effect on liver cells towards a decrease in the comet DNA index compared to the effect of MMS alone ($p<0.01$).

In the kidney cells of intact mice, the DNA comet index was 0.17±0.06. Under the influence of the infusion, diluted infusion, and herbal rosehip tea, the DNA comet index was at the negative control level. Most DNA comets have mainly been classified as classes I (0-6% DNA breaks). In kidney cells of mice under the MMS influence DNA comets have been classified as classes II-III. Under the combined influence of rosehips infusions with MMS, the IDC was statistically significantly ($p<0.01$) lower by 4.27-fold (infusion+MMS), 6.13-fold (herbal tea+MMS), 2.59-fold (diluted infusion+MMS) than of the positive control.

The DNA damage index (DI) in various studied organs is shown in the figure. In bone marrow cells, DI under the influence of MMS was 25.57; rosehip infusion – 1.86, rosehip herbal tea - 0.86, diluted rosehip infusion - 0.78, rosehip infusion+MMS – 4.71; rosehip herbal tea + MMS – 2.21; diluted rosehip infusion + MMS – 4.07. In spleen cells, DI under the influence of MMS was 19.18; rosehip infusion – 0.65; rosehip herbal tea – 1.41 and diluted 1/1 rosehip infusion – 1.92; rosehip infusion +MMS– 5.65; rosehip herbal tea +MMS – 3.35 and diluted 1/1 rosehip infusion + MMS – 6.06; The DI of genotoxic effect on liver cells for MMS was 21.80; 5.53 for MMS and rosehip infusion; 4.27 for MMS and rosehip herbal tea; 4.27 for MMS and 1/1 diluted rosehip infusion; 1.33 for rosehip infusion; 1.98 for rosehip herbal tea; 1.93 for diluted 1/1 rosehip infusion. In kidney cells, the indicators of genotoxic action, expressed by the damage index (DI), the following values were observed: MMS – 16.59; MMS and rosehip infusion – 3.88; MMS and rosehip herbal tea – 2.71; MMS and diluted 1/1 rosehip infusion – 6.41; rosehip infusion - 1.06; rosehip herbal tea – 1.41 and diluted 1/1 rosehip infusion – 1.97.



DNA damage Index in cells of different mice organs with separate
and combined with MMS and infusion, diluted infusion, and herbal tea of rosehip

In connection with the intensification of human economic activity and the expansion of the spectrum and the amount of various chemical compounds in the environment, protecting the organism from mutagenic factors has increased the genetic load in recent decades in populations. One of the promising directions is searching for natural protectors with some advantages over synthetic, medicinal preparations. In this regard, researchers' attention has increased to studying biologically active substances from medicinal plants, which may have antimutagenic and antioxidant activity. Natural antimutagens and antioxidants exhibit low toxicity and allergenicity, have a complex effect on the organism and do not cause side effects when used for a long time. Phytocompounds in plants have several biochemical and pharmacological properties, including antioxidant and anti-inflammatory, determining their anticarcinogenic and antimutagenic activity [17]. Phytocompounds can block carcinogenesis in the early stages and are an inexpensive, effective, and easily applicable approach in the fight against cancer [18]. The use of extracts, infusions, and herbal teas of plants with proven antimutagenic and antioxidant properties in everyday life is the most effective and affordable procedure for preventing oncological diseases [19].

In the conditions of a shortage of domestic herbal remedies, the search and comprehensive study of biologically active substances from plant raw materials in Kazakhstan is a timely and promising task. This problem's urgency is evidenced by the low degree of study of Kazakhstan's flora for antimutagenic and other activity types. Therefore, screening the republic's rich wild flora for various activity types, particularly antimutagenic, is a priority task. A comprehensive study of natural compounds' biological activity will expand knowledge about the mechanisms of regulation of growth processes, the reparation of genetic disorders, and the body's protection from the negative influence of environmentally hazardous factors. The source of various biologically active substances is herbal raw materials, which affect the body's metabolic and metabolic processes. In this regard, the wild rose, widespread throughout Kazakhstan's territory, is of great scientific interest. In rosehips, vitamins (A, C, E), coumarins, tannins, flavonoids (rutin, avicularin, quercitrin, isoquercitrin) are found. The antioxidant properties of tocopherols (vitamin E) are based on inactivating hydroxyl radicals [20]. *R. majalis* contains high ascorbic acid concentrations (vitamin C), a natural antioxidant and detoxifier that can remove almost all toxic compounds from the body. Flavonoids act as antioxidants and inactivate free radicals in the presence of metals [21, 22].

Thus, the results obtained indicate that MMS has a pronounced genotoxic activity. The DNA breaks frequency in mice that took only infusion, herbal tea, and diluted rosehip infusion in all studied organs' cells was at the control level. This indicates that the rosehip infusions in the concentrations used do not have genotoxic activity. The infusion, herbal tea, and diluted infusion changed the genotoxic effect of MMS in laboratory mice, which indicates the presence of antigenotoxic properties in rosehip infusions.

Conclusion. In this study, the medicinal rosehip (*R. majalis*) was studied in the form of an infusion, herbal tea, and diluted 1/1 infusion to evaluate genotoxic and antigenotoxic activity in laboratory mice using the Comet assay. It was found that rosehip infusions in different concentrations have no genotoxic activity on the internal organs (bone marrow, spleen, liver, kidneys) of animals. Infusion, herbal tea, and diluted 1/1 infusion of medicinal rosehips, when combined with MMS effects on mice, statistically significantly reduced the frequency of MMS-induced DNA breaks, which indicates the gene-protective activity of rosehips infusions. No statistically significant differences in the antimutagenic activity of the infusion, herbal tea, and diluted 1/1 rosehip infusion were found. Comparative analysis of the DNA damage index of the rosehip with MMS showed that the largest antimutagenic activity of rosehip infusions was manifested within the bone marrow cells and the smallest - within the spleen cells of laboratory animals.

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ROSACEAE ТУЫСТЫҒЫНДАҒЫ ИТМҰРЫН (*ROSA MAJALIS* HERRM.) ДӘРІЛІК ӨСІМДІГІНІҢ АНТИГЕНОТОКСИКАЛЫҚ ПОТЕНЦИАЛЫН ЗЕРТТЕУ

Аннотация. Ағзаның қоршаған ортаны ластаушы заттардың жағымсыз әсеріне төзімділігін арттыру медицинаның маңызды профилактикалық міндеттерінің бірі болып табылады. Осыған байланысты қазіргі кезде мутагендердің организмдегі әсерін жою немесе әлсірету үшін антитутагендерді белсенді іздеу жүріп жатыр. Өткен ғасырдың соңында өсімдіктер организмдерінің қатерсіз және қатерлі ісіктердің алдын алу мен емдеудегі антиоксидантты қасиеттерін дәлелдейтін көптеген зерттеулер жүргізілді. Өсімдіктерде кездесетін фитоқосындылар антиоксидантты және қабынуға қарсы, соның ішінде антиарциногендік және антимутагендік белсенділікке жауап беретін әр түрлі биохимиялық және фармакологиялық қасиеттерге ие. Раушангүлділер тұқымдасы (*Rosaceae*) дәрілік өсімдіктер ретінде қолданылатын өсімдік түрлеріне бай (жабайы раушан, өрмек, долана, қарасора, тау күлі, құс шиесі, шикілік, қара бүлдірген, құлпынай, таңқурай, бадам). Антимутагенді қосылыстардың перспективалы көздерінің бірі - *Rosa majalis Herrm* (итмұрын) дәрілік өсімдігі.

Біздің зерттеуіміздің мақсаты зертханалық тышқандарда итмұрын тұнбасының антигенотоксикалық потенциалын зерттеу болып табылады. Зерттеу жұмысының барысында BALB / c (*Mus musculus* Linn.) желісінің зертханалық тышқандары қолданылды. Зерттеу жұмысының объектісі ретінде итмұрын өсімдігінен тұнбасы, сұйылтылған 1/1 тұнбасы және шөп шайы алынды (*Rosa majalis* Herrm, *Rosaceae* тұқымдасы). Оң бақылау ретінде 40 мг / кг концентрациядағы метилметансульфонат (ММС, C2H6O3S) қолданылды. ММС стандартты қысқа мерзімді in vivo және in vitro сынақтарда мутагендік белсенділік көрсететін тікелей алкилдеуші агент. Итмұрын тұнбасының генотоксикалық және генопротекторлық белсенділігі зертханалық тышқандардың сүйек кемігі, көкбауыр, бауыр және бүйрек жасушаларында ДНҚ комета әдісінің сілтілі вариациясын қолдану арқылы зерттелді.

Зерттеу нәтижесінде қолданылған концентрациядағы итмұрын тұнбасы зертханалық тышқандардың сүйек кемігінің, көкбауырдың, бауырдың және бүйректің жасушаларына генотоксикалық әсер етпейтіні анықталды. Стандартты мутаген метилметансульфонаттың жануарларға енгізілуі ішкі ағзалардың барлық жасушаларында ДНҚ үзілістерін тудырды, олардың жиілігі бақылау деңгейіне қарағанда статистикалық тұрғыдан едәуір жоғары болды ($p < 0,01$). ММС-индуцирленген мутагенез деңгейі итмұрын және метилметансульфонат тұнбаларын біріктіріп енгізгенде статистикалық маңызды төмендеу көрсетті ($p < 0,01$). Итмұрын тұнбасын және мутагенді бірлесіп қабылдаған жануарлар ДНҚ-ның зақымдану индексін талдау көрсеткендей, дәрілік өсімдіктер тұнбасының генопротекторлық жоғары белсенділігі - сүйек кемігінің жасушаларында, ал ең азы - зертханалық тышқандардың көкбауыр жасушаларында болған. Әр түрлі тұнбалардың генопротекторлық белсенділігінде статистикалық маңызды айырмашылықтар болған жоқ. Алынған нәтижелер *R. majalis* тұнбасының антигенотоксикалық белсенділігін көрсетеді.

Түйін сөздер: итмұрын, мутаген, генотоксикалық, генопротектор, ДНҚ комета әдісі.

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ИЗУЧЕНИЕ АНТИГЕНОТОКСИЧЕСКОГО ПОТЕНЦИАЛА НАСТОЕВ ШИПОВНИКА (*ROSA MAJALIS* HERRM.) СЕМЕЙСТВА *ROSACEAE*

Аннотация. Повышение сопротивляемости организма к неблагоприятному воздействию различных загрязнителей окружающей среды является одной из важнейших профилактических задач медицины. В связи с этим в настоящее время ведется активный поиск антимутагенов для устранения или ослабления действия мутагенов в организме. В конце прошлого века было проведено множество исследований, доказывающих антиоксидантные свойства организмов растительного происхождения в профилактике и лечении доброкачественных и злокачественных опухолей. Фитосоединения, содержащиеся в растениях, обладают целым рядом биохимических и фармакологических свойств, включая антиоксидантные и противовоспалительные, которые обусловливают их антиканцерогенную и антимутагенную активности. Семейство розоцветных (*Rosaceae*) богато видами растений, используемых в качестве лекарственных растений (шиповник, кровохлёбка, боярышник, арония, рябина, черёмуха, лапчатка, ежевика, земляника, костяника, малина, миндаль). Одним из перспективных источников антимутагенных соединений является лекарственное растение *Rosa majalis* Herrm (шиповник).

Целью нашего исследования явилось изучение антигенотоксического потенциала настоев шиповника на лабораторных мышах. В работе были использованы лабораторные мыши линии BALB/c (*Mus musculus* Linn.). В качестве исследуемого вещества были взяты настой, настой разбавленный 1/1 и фиточай из растения шиповник (*Rosa majalis* Herrm, сем. *Rosaceae*). В качестве положительного контроля использовали метилметансульфонат (ММС, $C_2H_6O_3S$) в концентрации 40 мг/кг. ММС является алкилирующим агентом прямого действия, который в стандартных краткосрочных тестах in vivo и in vitro проявляет мутагенную активность. Генотоксическая и генопротекторная активность настоев шиповника была изучена с помощью щелочной вариации метода ДНК-комет в клетках костного мозга, селезенки, печени и почек лабораторных мышей.

В результате проведенного исследования установлено, что настои шиповника в использованных концентрациях не оказали генотоксического действия на клетки костного мозга, селезенки, печени и почек лабораторных мышей. Введение животным стандартного мутагена метилметансульфоната вызывало во всех клетках внутренних органов разрывы ДНК, частота которых статистически значимо превышала контрольный уровень ($p<0,01$). При совместном введении настоев шиповника и метилметансульфоната наблюдалось статистически значимое снижение ($p<0.01$) уровня MMS-индуцированного мутагенеза. Анализ индекса повреждения ДНК у животных, совместно принимавших настои шиповника и мутаген, показал, что наибольшая генопротекторная активность настоев лекарственного растения проявилась в клетках костного мозга, а наименьший - в клетках селезенки лабораторных мышей. Не выявлено статистически значимых различий в генопротекторной активности различных настоев. Полученные результаты указывают на антигенотоксическую активность настоев *R. majalis*.

Ключевые слова: шиповник, мутаген, генотоксичность, генопротектор, метод ДНК-комет.

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