Influence of the Herbal Preparation "Licorice Oil" on the State of Hematopoiesis in Rats Under Ionizing Irradiation

Marat Iztleuov*, Murat Teleuov, Yerbolat Iztleuov , Samat Saparbayev, Alma Yelubayeva, Gulmira Yemzharova, Sanimgul Sambayeva, Aigul Turganbayeva and Zhanat Umirzakova

West Kazakhstan Marat Ospanov Medical University. Aktobe, Kazakhstan.
*Corresponding Author E-mail: YerbolatIztleuovermar80@mail.ru

https://dx.doi.org/10.13005/bpj/2189
(Received: 14 January 2021; accepted: 14 June 2021)

The radioprotective effect of the herbal preparation "Licorice oil" on the hematopoietic system and oxidative stress was studied. The experiment was carried out on 30 male Wistar rats, divided into 3 groups. The first group is control group, the second is irradiation with 6Gy, third group - a week before irradiation and two weeks after, received "Licorice oil" intragastrically at a dose of 2.5 ml/kg of body weight. Gamma irradiation significantly reduced the number of erythrocytes, hemoglobin, hematocrit, leukocytes, thrombocytes in peripheral blood and bone marrow cellularity. The frequency of micronuclei in polychromatophilic erythrocytes of the bone marrow has significantly increased. The level of lipid peroxidation in the blood increased against the background of a significant decrease in the activity of antioxidant enzymes. The introduction of "Licorice oil" for 21 days provided a protective effect. In application of "Licorice oil", there was an increase in the number of cellular elements in the peripheral blood and against the background of a decrease in the frequency of micronuclei in the bone marrow. The activity of antioxidant enzymes in blood plasma increases against the background of a decrease in the amount of peroxidation products. The herbal preparation "Licorice oil" exhibits antioxidant activity, reduces genotoxicity and cytotoxicity under gamma irradiation. "Licorice oil" can be used to prevent radiation damage.

Keywords: Blood; Bone Marrow; Gamma Radiation; Micronuclei; Oxidative Stress; Phytopreparation "Licorice Oil;"

Radiotherapy is one of the most effective methods of treating malignant neoplasms. However, the side effects associated with radiotherapy limit its use. The most common side effect is suppression of the hematopoietic system, which is composed of rapidly proliferating precursor cells in the bone marrow. Hematopoietic injury causes myelosuppression and dose-dependent depletion of circulating blood cells, which lead to anemia and increased susceptibility to infection. Radiation exposure leads to dose-dependent defects in the lymphoid and hematopoietic systems through a complex cascade known as hematopoietic syndrome, which can lead to septicemia and death. It is well known that ionizing radiation also has an unprecedented long-term effect on cellular pathways, that leads to genomic instability, which can subsequently manifest itself in hereditary diseases or various forms of malignant neoplasms.
Ionizing radiation causes radiolysis of water in cells, resulting in the formation of highly reactive free radicals. Known as reactive oxygen species (ROS), they lead to a disproportion between prooxidants and antioxidants, causing oxidative damage to vital cellular structures, which leads to many pathological conditions. Consequently, free radicals and changes in vital structures require the development of countermeasures to minimize radiation damage. Protection of biological systems from ionizing radiation has paramount importance in case of planned as well as unplanned accidental exposure to radiation.

Many synthetic drugs have been tested in both in vitro and in vivo models to mitigate damage caused by ionizing radiation. However, at a clinically effective concentration (dose), they are toxic and cause side effects. In most cases, toxicity appears in promising radioprotective agents, which limits their usefulness and applicability.

Therefore, it is necessary to study alternative sources, especially natural ones, that will be used as effective and safe radioprotectors. Because of their low toxicity in an effective dose with minimal side effects, herbal products with antioxidant properties bind free radicals, leading to a minimum of radiation damage to normal tissues, are considered to be radioprotective.

The ability of bioactive phytocompounds to simultaneously have a multifactorial effect is unique. Among them, phytolipophilic drugs play a special role. They more easily penetrate cell membranes, have a higher activity and specificity of action, are stable and retain their pharmacological activity for a long time. One of them is a phytopreparation oil extract from licorice roots - “Licorice oil” (RK-M-#011042).

The ability of bioactive phytocompounds to simultaneously have a multifactorial effect is unique. Among them, phytolipophilic drugs play a special role. They more easily penetrate cell membranes, have a higher activity and specificity of action, are stable and retain their pharmacological activity for a long time. One of them is a phytopreparation oil extract from licorice roots - “Licorice oil” (RK-M-#011042).

Naked licorice (Glycyrrhiza glabza L.), due to its chemical composition, occupies one of the leading places among medicinal plants in terms of the scale of industrial collection, the breadth and value of the therapeutic effect. Licorice root preparations have a wide spectrum of pharmacological action - antioxidant, wound healing, antiallergic, antimutagenic, antiviral, antitumor, anti-inflammatory, antimicrobial, immunotropic, hepatoprotective, antidote, etc.

And the main medicinal properties are due to the composition of its root: glycyrrhizic and glycercetic acids (6-23%); flavonoids (about 30%) - liquiditin, licurazide, quercetin and others (up to 5.3%); mono- and disaccharides (up to 20%); pectins (4-6%); phenol carboxylic acids; coumarins (up to 2.5%); alkaloids; essential oil (up to 0.03%); steroids (extriol); organic acids (up to 4.3%); macro- and microelements.

The main active ingredient of licorice root is the triterpene saponin glycyrrhine, which is, in active form, mixed potassium-calcium-magnesium salts of tribasic glycyrrhizic acid. It has been established that glycyrrhizic acid has anti-inflammatory, antiallergic, antiviral, hepatoprotective, immunomodulatory, antiulcer effects, and has antioxidant properties. In addition, the presence of hydrophilic and hydrophobic fragments in the glycyrrhizic acid molecule gives it unique surface-active and gel-forming properties that contribute to the expansion of the spectrum of biological activity.

An oil extract of licorice has been developed and patented in Kazakhstan. The antioxidant properties of “Licorice oil” have been studied, as a result of which the drug is recommended for the prevention and complex treatment of diseases characterized by an increase in the intensity of lipid peroxidation and has a corrective effect on the Krebs cycle in the lungs. However, there is no detailed study of the effect of licorice root extract, especially the herbal preparation “Licorice Oil”
on oxidative stress and hematopoietic systems, while hematopoietic syndrome is considered the main cause of death in animals after general body irradiation. Thus, finding them above, the present study was conducted to study the role of the herbal remedy “Licorice oil” in mitigating the adverse radiation effects on the blood system and oxidative stress.

**MATERIAL AND METHODS**

The work was performed on 30 male Wistar rats weighing 170-190 g. The animals were kept in standard conditions in the vivarium of the Scientific and Practical Center of the Non-Commercial Joint Stock Company “West Kazakhstan Marat Ospanov Medical University” (Aktobe, Republic of Kazakhstan) on a standard diet with free access to food and water. The experiments were carried out in accordance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Purposes (Strasbourg, 1986). The experiment program was discussed and approved by the regional ethical commission of the university.

10 days after acclimatization, the rats were randomly divided into 3 groups: group 1 - control, group 2 - irradiation, group 3 - before and after irradiation, which received the drug “Licorice oil” intragastrically at a dose of 2.5 mg / kg of body weight.

The dosage of the herbal preparation “Licorice oil”, the method of application and the duration of use is justified by the literature data. The process of irradiation of animals of groups 2 and 3 was carried out on a Teragam radiotherapy device (Czech Republic) with total gamma rays of 60Co at a dose of 6 Gy, with a power of 0.54 Gy/ min. The distance from the source to the skin of animals is 70 cm.

Animals in all groups are euthanized at the end of the experimental period by instant decapitation under light ether anesthesia to prevent stress. Part of the blood was collected in tubes with EDTA, an anticoagulant, and centrifuged at 2200g for 10 min. Collected plasma samples were stored at - 20°C. Erythrocytes obtained from blood samples were washed three times with 5 volumes of phosphate-buffered saline (pH -7.4) by centrifugation at 1500 rpm. Storage at –80°C. Another part of the blood was collected for biochemical analysis.

Hematological analysis. The cellular composition of the blood was studied using a BF-580 hematological analyzer (China). The bone marrow cellularity was determined by flushing the bone marrow from the femur and calculating the number of cells (myelokaryocytes) per femur in the Goryaev chamber according to the standard method.

Micronuclear analysis. Micronucleus in the bone marrow: the preparation of the test preparations was carried out by the standard method. A smear was made from a suspension prepared for cytogenetic preparations and stained by the Papenheim method using the May-Grunwald fixative and Giemsa paint. The resulting preparations were encrypted and subjected to microscopic cytogenetic analysis. The number of micronuclei (MN) in polychromatophilic erythrocytes (PCE) of the bone marrow was counted. Analyzed - 3000 PCEs from each animal.

Biochemical analysis. Lipid peroxidation. Determination of diene conjugates (DC) was carried out by a generally accepted method modified by the ultraviolet spectrum of the first oxidation products of polyunsaturated lipids with an absorption maximum at 233 nm; the molar extinction coefficient is 2,210-1cm-1. The content of DC was expressed in units of optical density (ODU) per ml (ODU/ml). The content of malonic dialdehyde (MDA) was determined using thiobarbituric acid (TBA) according to a modified method. The principle of the method: at high temperatures in an acidic medium, MDA reacts with 2-TBA to form a colored trimethine complex with an absorption maximum at 532 nm. The MDA level was expressed in ìmol/L.

Antioxidant blood defense system. The content of sulfhydryl (SH) groups in blood plasma was determined by the method. The amount of thionitrophenyl anion formed in the sample is directly proportional to the amount of SH-groups that reacted with 5,5– dithiobis. After 40 minutes, the optical density of the sample was measured spectrophotometrically at 412 nm. The number of SH groups was expressed in ìmol/L. The serum glutathione (GSH) level was determined according to the method modified in ìmol/L.

Catalase activity (CAT) was measured...
by the method\(^{30}\). The reaction was started by the addition of 2.0 ml of hydrogen peroxide to 10 lll of the hemolysate and, after 10 minutes, was stopped by the addition of 1.0 ml of 4% ammonium molybdate. The absorbance of the sample was measured at 410 nm. The enzyme activity was expressed in units of activity per mg protein (U min/mg protein). One unit of catalase activity was defined as the activity to decompose 1 ìmol of hydrogen peroxide per minute (60s).

Superoxide dismutase (SOD) activity in erythrocytes was determined by the method\(^{4}\). As a unit of SOD activity, we took the amount of enzyme necessary to inhibit the decrease in nitroblue tetrazolium (NBT) by 50%, and the activity was expressed as U/mgPt.

The activity of glutathione peroxidase (GPx) was determined by the method\(^{39}\) by the oxidation of NADPH•H2 in the conjugated glutathione reductase reduction reaction on a spectrophotometer at 340 nm. Results are expressed as nmol oxidized NADPH min/mg protein or U min/mg protein. Protein content was determined by the method of Lowry et.al.\(^{40}\).

Statistical analysis. The results are expressed as mean values. The significance of the differences in mean values was assessed using the Student and Wilconson – Mann – Whitney tests. Differences were considered statistically significant at r<0.05.

**RESULTS AND DISCUSSIONS**

Gamma irradiation (6 Gy) led to a pronounced and persistent change in the peripheral blood picture, caused mainly by the emptying of the bone marrow (table 1), which is characterized by a decrease in the level of cellular elements in the blood and bone marrow cellularity by 41%, 50%, 25%. 42%, 35% and 46% compared to the control group. Prophylactic and therapeutic use of the drug “Licorice oil” caused a significant increase in the peripheral blood of the number of cellular elements and bone marrow cellularity by 25%, 34%, 19%,

| Table 1. Influence of “Licorice oil”, gamma-irradiation on the parameters of peripheral blood and bone marrow cellularity in male rats. (mean ± standard deviation - M ± σ, n = 10) |
|---|---|---|---|---|---|---|
| RBS | İB | HTC (%) | WBC | PLT | Bone marrow cellularity |
| Control | 5.3±0.945 | 124±25.303 | 40.3±4.444 | 8.1±1.265 | 449±91.644 | 262±41 |
| γ- irradiated rats (IRR) | 3.12±0.729\(x\) | 62±11.015\(x\) | 30.3±6.312\(x\) | 4.7±1.899\(x\) | 290±82.172\(x\) | 142±25.2\(x\) |
| “Licorice oil” | 3.99±0.79\(o\) | 83±15.779\(o\) | 36.16±7.585 | 6.53±0.949\(o\) | 386±69.674o | 195±34.09o |

Note: x - p<0.05 in comparison with control data; 0 - p<0.05 compared with data from irradiated rats

| Table 2. Influence of “Licorice oil” on the formation of micronuclei in erythrocytes of the bone marrow in rats exposed to 6 Gy gamma radiation. (1± σ in a group of 10 rats) |
|---|---|---|---|
| Group | Indicators | Number of analyzed cells | The number of cells with micronuclei, % |
| Control | Number of analyzed cells | 3000 | 4.32±1.044 |
| γ- irradiated rats (IRR) | 3000 | 21.6±4.734\(x\) |
| “Licorice oil” | 3000 | 11.26±2.853\(o\) | 48% |

Note: Each value represents the mean ± standard deviation (M ± σ) of 10 animals; x - p <0.05 in comparison with control data; 0 - p<0.05 compared with the data of irradiated rats; the antimitogenic effect was calculated using the formula - AME = \(\frac{M_1-M_2}{M_1}\) x 100, M1 - the number of cells with micronuclei under ã-ray irradiation; M2 - the number of cells with micronuclei with the introduction of “Licorice oil” (a week before and two weeks after irradiation).
Table 3. Influence of “Licorice oil” on oxidative stress in rats with gamma irradiation

| DC  | MDA   | SH-gr | GSH   | SOD   | Cat   | GPx   |
|-----|-------|-------|-------|-------|-------|-------|
| Control | 1.1±0.25 | 1.9±0.173 | 3.6±0.733 | 20.6±19.3 | 1.3±0.3 | 1.2±0.3 |
| γ-irradiated rats (IRR) | 1.7±0.3 | 2.2±0.3 | 2.0±0.4 | 2.0±0.4 | 1.7±0.3 | 1.3±0.3 |
| “Licorice oil” | 1.3±0.3 | 1.4±0.3 | 2.3±0.3 | 2.7±0.3 | 1.3±0.3 | 1.3±0.3 |

Note: x - p <0.05 in comparison with the data of the control group; 0 - p<0.05 - compared with the data of irradiated animals. Each value represents the mean ± standard deviation (M ± σ) of 10 animals.

39%, 33% and 37%, respectively, compared with the data of the irradiated group.

Micronucleus test. The effect of gamma irradiation and the results of the protective action of the herbal preparation “Licorice oil” on PCE with micronuclei in the bone marrow are presented in Table 2. Single total g-irradiation at a dose of 6 Gy is accompanied by the induction of cytogenetic disorders in the cells of the bone marrow, which is manifested by an increase in micronuclei in the erythrocytes of the bone marrow 5.0 times (21.6±4.734, %o) in comparison with the control data.

The increase in the rate of formation of micronuclei was 500%. With the therapeutic and prophylactic use of Licorice Oil, the frequency of micronuclei in polychromatophilic erythrocytes of the bone marrow decreased in comparison with the data of the irradiated (11.26±2.85 %o). This indicator statistically differed from the clastogenic effect of gamma irradiation (6 Gy) (p <0.001), and the reduction was 48%. The rate of micronucleus formation decreased 1.9 times as compared to the data of irradiated animals. Therefore, we can conclude that the prophylactic and therapeutic use of the herbal remedy “Licorice oil” has shown the ability to modulate the mutagenesis induced by gamma radiation in the direction of reducing the damaging effect. The antimutagenic effect was 48%.

The data presented in table 3 showed that whole body gamma irradiation in rats resulted in a significant decrease in the activity of antioxidant enzymes in erythrocytes. The activity of superoxide dismutase, catalase and glutathione peroxidase decreases by 20%, 30% and 46%, respectively, in comparison with the data of the animals of the control group. Also, the concentration of GSH and SH-groups in the blood decreases significantly, respectively, by 27% and 25% against the background of an increase in the level of diene conjugates and malonic dialdehyde in plasma by 60% and 29%, respectively, in comparison with the control. Therapeutic and prophylactic administration of the herbal preparation “Licorice oil” caused an increase in the activity of erythrocyte enzymes SOD, CAT, GPO, the content of GSH and SH blood groups by 21%, 26%, 71%, 30% and 26%, respectively, and a decrease in the level of DC and MDA in blood plasma by 26% and
Iztleuov et al. Biomed. & Pharmacol. J., vol. 14(2), 869-879 (2021)

Ionizing radiation has negative health effects, including dysfunctions of the hematopoietic system, immune dysfunction, genetic mutations, and oxidative stress. Radiation damage resulting from the formation of reactive oxygen species is the result of oxidative damage to vital cellular molecules and structures, including proteins, lipids, DNA, and membranes by free radicals (ROS). In order to achieve the best therapeutic effect during the treatment of tumors, normal tissues must be protected from radiation damage. Therefore, the development of antioxidant-based biologics is necessary to prevent and/or treat radiation hazards.

In the present study, the radioprotective effect of the herbal preparation “Licorice oil” was studied. Ionizing radiation has well-documented effects on blood cells, and suggests that these effects contribute to the hematopoietic syndrome observed in animals and humans after exposure to general body radiation. Hematopoietic syndrome is considered the leading cause of death in animals after general body irradiation and mainly occurs within 30 days after exposure. In the present study, the levels of erythrocytes, hemoglobin, hematocrit, leukocytes, and platelets were reduced in rats irradiated with α-radiation compared with control, which indicates erythropenia, leukopenia, and thrombocytopenia in these animals.

Depletion of the bone marrow is observed (bone marrow cellularity decreased by 46% in comparison with the control data). Bone marrow cellularity most adequately characterizes the degree of radiation damage to the body. Bone marrow depletion, caused by direct destruction of hematopoietic stem cells, and a decrease in the incorporation of iron and hemoglobin binding to the erythrocyte membrane, resulting in anemia. Our results showed that the use of “Licorice oil” before and after irradiation led to an increase in the number of erythrocytes, hemoglobin, hematocrit, leukocytes, and platelet content compared with the levels in the irradiated animals. The bone marrow cellularity increased by 37% in comparison with the data of the irradiated animals. All this indicates a hemo-stimulating effect. The hemo-stimulating effect of the phytopreparation can be associated with both increased proliferation, the activity of surviving stem cells, and migration to the bone marrow from the peripheral blood and thymus. Research by T.G. Razina showed that glyceram, which is a monoammonium salt of glycyrrhizic acid, stimulates granulo- and erythrocytopoiesis under conditions of hemodepression. Guryantseva L.A. et al. in their experiments found that glyceram normalizes the structural and functional organization of the bone marrow, providing intensive maturation of colony-forming units under conditions of myelosuppression caused by the administration of cyclophosphamide.

To date, enough information has been collected on the role of free radicals in the mechanism of induced mutations. Our results showed that total gamma irradiation of the whole body of animals leads to the induction of cytogenetic abnormalities in bone marrow cells, which is manifested by an increase in the frequency of micronuclei in polychromatophilic bone marrow erythrocytes. Phytopreparation “Licorice oil”, when administered before and after irradiation, significantly reduces the amount of micronuclei. The anti-mutagenic effect was 48%.

Our results show that whole body gamma irradiation led to a significant increase in the level of DC in the blood plasma and a marker of LPO intensity - MDA in the blood plasma, as well as a significant decrease in the activity of SOD, CAT, GPO in erythrocytes, and a decrease in the GSH and SH groups in the blood. This decrease is caused by damage to cell membranes and changes in dynamic membrane permeability due to increased peroxidation after irradiation, release of intracellular enzymes into the bloodstream, and increased use of antioxidant enzymes in the body to detoxify radiation free radicals. These results, characterizing the intensity of oxidative stress, are consistent with previous results. Reduced glutathione, blood SH-groups, thiol constituents of the second line of cellular defense of the antioxidant system (AOS) act as a direct reactive scavenger of free radicals. A decrease in the levels of GSH, SH-groups reflects their increased need for cells to combat reactive oxygen species formed after irradiation. However, a decrease in GPX activity may be associated with a decrease in the availability of GSH, which is a GPX substrate and is required for catalysis.

The introduction of “Licorice oil” before
and after irradiation reduced the content of DC and MDA in the blood. The mechanisms by which a phytopreparation inhibits lipid peroxidation most likely include direct scavenging of initiating radicals. In our previous studies, it was shown that the drug “Licorice oil” plays an important role in the prevention of chromium-induced oxidative stress, and enhancement of the cellular antioxidant system of the blood and exhibits hemorheological and antioxidant activity. Also, among workers of chromium production, the use of “Licorice oil” activates the compensatory reactions of the body aimed at inhibiting lipid peroxidation, stimulates antiradical activity.

The introduction of “Licorice oil” before and after irradiation reduced the content of DC and MDA in the blood. The mechanisms by which a phytopreparation inhibits lipid peroxidation most likely include direct scavenging of initiating radicals. In our previous studies, it was shown that the drug “Licorice oil” plays an important role in the prevention of chromium-induced oxidative stress, and enhancement of the cellular antioxidant system of the blood and exhibits hemorheological and antioxidant activity. Also, among workers of chromium production, the use of “Licorice oil” activates the compensatory reactions of the body aimed at inhibiting lipid peroxidation, stimulates antiradical activity.

The positive effect of the herbal remedy “Licorice oil” is a systemic manifestation of a number of mechanisms. Apparently, we can talk about an antistress effect, including a stabilizing effect on certain links of hematopoiesis, it is possible that biochemically active compounds of a phytopreparation can act as a “trap” of free radicals, thirdly, about an immunomodulatory effect. The formation of a certain relationship in the hypothalamo-pituitary-adrenal system under the influence of the nootropic properties of “Licorice oil” contributes to the inclusion of protective mechanisms that determine, together with immunomodulatory, antioxidant, antimutagenic, the body’s resistance to the effects of α-irradiation.

CONCLUSION

Thus, our results show that the herbal preparation “Licorice oil” exhibits antioxidant activity, reducing the production of free radicals and restoring the imbalance of prooxidant-antioxidant homeostasis during therapeutic and prophylactic use. Apparently, the explanation of the observed changes in antioxidant homeostasis after the introduction of “Licorice oil” is that the phytopreparation increases the power of the antioxidant system in neutralizing and removing the formed radicals of oxidative stress. The drug reduces the level and intensity of lipid peroxidation, has an anti-mutagenic effect. Phytopreparation “Licorice oil” has a hemo-stimulating effect on the blood system, manifested in an increase in the cellular components of blood and bone marrow cellularity, due to the stimulation of migration, proliferation and maturation of hematopoietic cells.

It can be assumed that the protective effect of the phytopreparation is mainly due to the presence of glycyrrhizic acid in its composition, which has a corticoid effect, maintaining at a higher level the process of energy supply to the structures responsible for the implementation of the adaptive reactions of the organism.

The results of this study show that under conditions of therapeutic and prophylactic use (before and after irradiation), Licorice Oil controls the production of free radicals and protects against oxidative damage by inhibiting blood lipid peroxidation and enhancing the antioxidant system.

We assume that Licorice Oil, due to its multifaceted influence, may represent a promising radioprotector that deserves an integral assessment of its antiradiation effect.

ACKNOWLEDGEMENT

I express my gratitude to the staff of the clinical laboratory and vivarium, the staff of the radiation therapy department, and the university administration.
Conflict of interest
No conflicts of interest.

Funding source
The funds were allocated by the university free of charge within the framework of a research grant.

REFERENCES
1. Aldiyarova N.T. Anti-inflammatory and analgesic activity of licorice oil. Pharmacy Kazakhstan.; 1:29-30 (2006)
2. Andreeva L.I., Kozhemiakin L.A., Kishkun A.A. [Modification of the method of determining lipid peroxidation in a test using thiobarbituric acid]. La Delo.; 11:41-3 (1988).
3. Arora R., Gupta D., Chawla R., Sagar R., Sharma A., Kumar R., Prasad J., Singh S., Samanta N., Sharma R.K. Radioprotection by plant products: present status and future prospects. Phytother Res. 19(1):1-22 (2005). doi: 10.1002/ptr.1605.
4. Beauchamp C., Fridovich I. Superoxide dismutase: improved assays and an assay applicable to acrylamide gels. Anal Biochem.; 44(1):276-87 (1971). doi: 10.1016/0003-9861(71)90370-8.
5. Bekenova Zh.M. Substrate - enzyme relationships of the products of the Krebs cycle in the lungs of rats upon inhalation of uranium ore dust and the use of Valeolegiya licorice extract.; 3: 76-79 (2009).
6. Bhosle S.M., Huigol N.G., Mishra K.P. Enhancement of radiation-induced oxidative stress and cytotoxicity in tumor cells by eflagic acid. Clin Chim Acta.; 359(1-2):89-100 (2005). doi: 10.1016/j.cca.2005.03.037.
7. Billings P.C., Romero-Weaver A.L., Kennedy A.R. Effect of Gender on the Radiation Sensitivity of Murine Blood Cells. Gravit Space Res.; 2(1):25-31 (2014).
8. Boerma M., Hauer-Jensen M. Preclinical Research into Basic Mechanisms of Radiation-Induced Heart Disease. Cardiol Res Pract.; 858262 (2011). doi: 10.4061/2011/858262
9. Booth C., Tudor G., Tudor J., Katz B.P., MacVittie T.J. Acute gastrointestinal syndrome in high-dose irradiated mice. Health Phys.; 103(4):383-99 (2012). doi: 10.1097/HP.0b013e31828b6ee13.
10. Cadet J., Bellon S., Douki T., Frelon S., Gasparutto D., Muller E., Sauvaigo S. Radiation-induced DNA damage: formation, measurement, and biochemical features. J Environ Pathol Toxicol Oncol.; 23(1):33-43 (2004). doi: 10.1615/jenvironpathoxoncol.v23.i1.30.
11. Chandresh Shyam, Devinder Dhawan, Vijayta Chadha. In vivo radioprotective effects of wheatgrass (Triticum aestivum) extract against X-irradiation-induced oxidative stress and apoptosis in peripheral blood lymphocytes in rats. Asian Journal of Pharmaceutical and Clinical Research. 11(4):239 (2018). DOI:10.22159/ajpcr.2018.v11i4.23741.
12. Collins R.A., Howard C.J., Duggan S.E., Werling D. Bovine interleukin-12 and modulation of IFN gamma production. Vet Immunol Immunopathol. 68(2-4):193-207 (1999). doi: 10.1016/s0165-2427(99)00020-3.
13. Dainiak N. Hematologic consequences of exposure to ionizing radiation. Exp Hematol. 2002; 30(6):513-28. doi: 10.1016/s0301-472x(02)00802-0.
14. Dzhumasheva R.T. Mustafina R.Kh. Âëèÿíèå îáåçîâàëèíèå êëàññåé òîé îòëîãè÷å íàãî íà íóáêîíîâëåé èõîâåéíîîñòíîé íåíîíîâ ÀÈ/ÀÇ íîòí èîëèéìåé âåëèïõîâî÷å òîñïåðèé â Àãîòàáà îáåçîâåéíîîñòíîé ãîëîááåé. 3(61): 85-86 (2010).
15. Dzhusipova A.K., Arystanov A.Zh. âÁäíàëåéöàáîí íàãî íàãîâåéíîå èëèìîëåéìåé íîãî-àëåáöàáîíîå ìîãàâàìåöà íå ñêîëüíûé íå ñêîëüíûé íà äàëüöåé. Îáîçàìåòëåé–äåìåéñòâóþùèé. 2005. – ÿîä-àëåáöàáîí: 20-32.
16. El-Dessouky W.I, Mahmoud A.H., Abbas M.M. Antioxidant potential and hypolipidemic effect of whey protein against gamma irradiation induced damages in rats. Appl Radiat Isot. 129:103-107 (2017 ). doi: 10.1016/j.apradiso.2017.07.058.
17. Ellman G.L. Tissue sulfhydryl groups. Arch Biochem Biophys. 82(1):70-7 (1959). doi: 10.1016/0003-9861(59)90090-6.
18. Eshak M.G., Osman H.F. Role of moringa oleifera leaves on biochemical and genetical alterations in irradiated male rats. Middle East Journal of Scientific Research. 16(10):1303-1315 (2013). DOI:10.5829/idosi.mejsr.2013.16.10.7659.
19. Gavrilov, V.B. and Mishkorudnaya, M.I., Spectrophotometric determination of blood plasma lipid hydroperoxides. Lab. Delo, 3: 33–35 (1983).
20. Guo C.Y., Luo L., Urata Y, Goto S., Huang W.J., Takamura S., Hayashi F., Doi H, Kitajima Y., Ono Y., Ogi T, Li T.S. Sensitivity and dose dependency of radiation-induced injury in peripheral blood lymphocytes in rats. Asian Journal of Pharmaceutical and Clinical Research. 11(4):239 (2018).
21. Guryantseva L.A. Udut V.V., Semanina E.V., Khirkhova T.Yu., Zhadanova V.V. Mechanisms of regulation of the blood system under the influence of hemostimulants against the background of cytostatic myelosupression. Siberian Journal of Oncology. 3 (15): 39-43 (2005).
IZTLEUOV et al., Biomed. & Pharmacol. J, Vol. 14(2), 869-879 (2021)

22. Ilyinsky N.N. Novitsky V.V. and Vanchugova N.N. Micronucleus analysis and cytogenetic instability. Tomsk, 213 (1991).

23. Ismail A.F., El-Sonbaty S.M. Fermentation enhances Ginkgo biloba protective role on gamma-irradiation induced neuroinflammatory gene expression and stress hormones in rat brain. *J Photochem Photobiol B.*; 158:154-63 (2016). doi: 10.1016/j.jphotobiol.2016.02.039.

24. Iztleuov Ye.M., Mamyrbaev A.A., Iztleuov M.K. Effect of oil extract from licorice roots on nonrespiratory lung function in workers of chromium production. Materials of the scientific and practical conference. *Astanan.* 84-86 (2014).

25. Iztleuov M.K., Iztleuov Ye.M., Zinalieva A.N., Iztleuova U., Iztleuova G.M. Effect of oil extract from licorice roots on stress-induced damage to organs and systems in rats. Materials of the international scientific and practical conference. *Astanan.* Moscow, 67-71 (2013).

26. Iztleuov M.K., Iztleuov Ye.M. Effect of oil extract from licorice roots on stress-induced toxicity in rats. Materials of the international scientific and practical conference. *Astanan.* Moscow, 27-29 (2016).

27. Jagetia G.C., Venkatesha V.A. Mangiferin protects human peripheral blood lymphocytes against a-radiation-induced DNA strand breaks: a fluorescence analysis of DNA unwinding assay. *Nutrition Research.* 26:303-311 (2006).

28. Jollow DJ, Mitchell JR, Zampaglione N, Gillette JR. Bromobenzene-induced liver necrosis. Protective role of glutathione and evidence for 3,4-bromobenzene oxide as the hepatotoxic metabolite. *Pharmacology.*; 11(3):151-69 (1974). doi: 10.1159/000136485.

29. Koroliuk MA, Ivanova LI, Ma-orova IG, Tokarev VE. [A method of determining catalase activity]. *Lab Delo.*; 1:16-9 (1988).

30. Kosmagambetov A. Zh. Influence of “Licorice oil” on the content of antioxidant vitamins retinol and tocopherol. *Astanan medicine journals.* 4: 65-67 (2000).

31. Kosmagambetov A. Zh., Kalieva K. D. Antioxidant properties of “Licorice oil” // Medicine. – 2000. – 4. – N. 57–58.

32. Krishna A., Kumar A. Evaluation of radioprotective effects of Rajgira (Amaranthus paniculatus) extract in Swiss albino mice. *J Radiat Rex.*; 46(2):233-9 (2005). doi: 10.1269/jrr.46.233.

33. Kuntiae VS, Stunkoviae MB, Vujiae ZB, Brboriae JS, Uskokoviae-Markoviæ SM. Radioprotectors - the evergreen topic. *Chem Biodivers.*; 10(10):1791-803 (2013). doi: 10.1002/cbdv.201300054.

34. Kuzdenbaeva R.S, Imambaev S.E. Kosmagambetov A. Zh. The nature of nutrition and antioxidant activity of phytopreparations. *Aktobe,* 116 (2000).

35. Lee S.Y., Kim Y.K., Park N., Kim C.S., Lee C.V., Park S.U. Chemical constituents and biological activities of the berry of Panax ginseng. *Journal of Medicinal Plants Research,* 4(5), pp. 349-353 (2010).

36. Li M, You L, Xue J, Lu Y. Ionizing Radiation-Induced Cellular Senescence in Normal, Non-transformed Cells and the Involved DNA Damage Response: A Mini Review. *Front Pharmacol.* 22;9:522 (2018). doi: 10.3389/fphar.2018.00522.

37. Li YR, Cao W, Guo J, Miao S, Ding GR, Li KC, Wang J, Guo GZ. Comparative investigations on the protective effects of rhodioside, ciwujianoside B and astragaloside IV on radiation injuries of the hematopoietic system in mice. *Phytother Res.* 25(5):644-53 (2011). doi: 10.1002/ptr.3313.

38. Little C, Olinescu R, Reid KG, O’Brien PJ. Properties and regulation of glutathione peroxidase. *J Biol Chem.*; 245(14):3632-6 (1970).

39. Lowry OH, ROSEBROUGH NJ, FARR AL, RANDALL RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem.* 1951 Nov;193(1):265-75.

40. Mansaveena V., Akula K.K., Sangram V. A comparative evaluation of enzymatic antioxidant levels in pre and post therapy patients with oral cancer. International Journal of Pharmacy and Pharmaceutical Sciences. 2014. 6(11):52-56

41. Mansour HH, Hafez HF, Fahmy NM, Hanafi N. Protective effect of N-acetylcysteine against radiation induced DNA damage and hepatic toxicity in rats. *Biochem Pharmacol.* 2008 Feb 1;75(3):773-80. doi: 10.1016/j.bcp.2007.09.018.

42. Mauch P, Constine L, Greenberger J, Knoesp W, Sullivan J, Liesveld JL, Deeg HJ. Hematopoietic stem cell compartment: acute and late effects of radiation therapy and chemotherapy. *Int J Radiat Oncol Biol Phys.* 1995 Mar 30;31(5):1319-29 (2005). doi: 10.1269/ jrr.46.233.

43. Mettler FA Jr, Voelz GL. Major radiation exposure—what to expect and how to respond. N Engl J Med. 2002 May 16;346(20):1554-61. doi: 10.1056/NEJMra000365.
46. Muravyova I, Khadzhieva ZD, Mandzhigoladze T Yu. Study of the possibility of expanding the range of dosage forms of licorice root preparations. Physiology - biochemical aspects of the radiation of medicinal plants. Novosibirsk, 1998. – p. 134-138.

47. Mukushova G D, Sundetov Zh S, Iztleuov M K, Suleimenova R, Isaeva B. The effect of red licorice oil on the circulatory system in the development of chromium poisoning. Topical issues of pathophysiology and medicine. Almaty; Evero, 2008; 41-46.

48. Mustafina R Kh, Dzhumasheva R T, Kazymbet P K. Dose-time changes in the content of malondialdehyde in the lungs upon inhalation of uranium ore dust and the use of licorice extract. Astana medicine journal. 2007; 95-99.

49. Nakajima N, Utsunomiya T, Kobayashi M, Herndon DN, Pollard RB, Suzuki F. In vitro induction of anti-type 2 T cells by glycyrrhizin. Burns. 1996 Dec;22(8):612-7. doi: 10.1016/s0305-4179(96)01154-5.

50. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, Sakata R, Sugiyama H, Kodama K. Studies of the mortality of atomic bomb survivors, Report 14, 1950-2003: an overview of cancer and noncancer diseases. Radiat Res. 2012 Mar;177(3):229-43. doi: 10.1667/RR1399.1. Epub 2011 Dec 15.

51. Paolini M, Pozzetti L, Sapone A, Cantelli-Forti G. Effect of licorice and glycyrrhizin on murine liver CYP-dependent monooxygenases. Life Sci. 1998;62(6):571-82. doi: 10.1016/s0024-3205(97)01154-5.

52. Patyar RR, Patyar S. Role of drugs in the prevention and amelioration of radiation induced toxic effects. Eur J Pharmacol. 2018 Jan;15385;207-216. doi: 10.1016/j.ejphar.2017.12.011.

53. Pavelkovskaya G P. Phytopharmacy is one of the areas of bioinformatic medicine. Pharmacy of Kazakhstan. - 2005; -7:12-14.

54. Pavlova S I., Uteshev B S., Sergeev A V. Liquorice root. Possible mechanisms of antitoxic, anticarcinogenic and antitumor properties (review) Chem. Pharm. Magazine.2003; 37:6: 36-39.

55. Placer Z. Lip peroxidation systeme im biologischen material. Nahrung. 1968; Bd. 12(6): 679-684.

56. Rai M K. Herbal medicines in India; retrospect and prospect. Fittoterapia (1994) 65 483-491.

57. Razina T A. Phytopreparations and biologically active substances of medicinal plants in the complex therapy of malignant neoplasms (experimental studies): Abstract. Tomsk, 2006; 40 ff.

58. Reza Ghassemnezhad Targhi, Mansour Homayoun, Somaich Mansouri, Mohammad Soukhtanloo, Shokouhazam Mansour, Soleymanifard, Masoumeh Segeratolam. Radio protective effect of black mulberry extract on radiation-induced damage in bone marrow cells and liver in the rat. Radiation Physics and Chemistry. Volume 130, January 2017, Pages 297-302.

59. Rosen EM, Day R, Singh VK. New approaches to radiation protection. Front Oncol. 2014; 20:4:381. doi: 10.3389/fonc.2014.00381.

60. Rosenzweig SD, Holland SM. Congenital defects in the interferon-gamma/interleukin-12 pathway. Curr Opin Pediatr. 2004 Feb;16(1):3-8. doi: 10.1097/00008480-200402000-00003.

61. Saada H N, Ussama Z S, Madhy A M. Effectiveness of Aloe vera on the antioxidant status of different tissues in irradiated rats. Pharmazie. 2003 Dec;58(12):929-31.

62. Sakhanova S K. Influence of oil phytopreparations on indicators of energy metabolism in experimental amnesia. Medical sciences. 2010; 6: 47-49.

63. Sakhanova S K., Berdgaleeva A K. Study of the nootropic activity “Licorice oil” in the experiment. XVI Russian National Congress “Man and Medicine”. Moscow, 2009; 735.

64. Sangsuwan T, Haghdooost S. The nucleotide pool, a target for low-dose gamma-ray-induced oxidative stress. Radiat Res. 2008 Dec;170(6):776-83. doi: 10.1667/RR1399.1.

65. Sayed AA, Abbass OA, Saad MA, Marie MS. Cicer arietinum extract ameliorate α-irradiation disorders via modulation of oxidative/antioxidative pathway. J Photochem Photobiol B. 2018 Jun;183: 46-56. doi: 10.1016/j.jphotobiol.2018.04.015.

66. Schmid W. The micronucleus test. Mutat. Res.; 31: 9-15 (1975).

67. Scibior D, Skrzyczki M, Podsia M, Czeczot H. Glutathione level and glutathione-dependent enzyme activities in blood serum of patients with gastrointestinal tract tumors. Clin Biochem.; 41(10-11):852-8 (2008). doi: 10.1016/j.clinbiochem.2008.03.005.

68. Shim S B., Kim N J., Kim D H. Beta-glucuronidase inhibitory activity and hepatoprotective effect of 18 beta-glycyrrhetinic acid from the rhizomes of Glycyrrhiza uralensis. Planta Med.; 66(1):40-3 (2000). doi: 10.1055/s-2000-11109.

69. Soliman AF, Saif-Elnasr M, Abdel Fattah SM. Platelet-rich plasma ameliorates gamma radiation-induced nephrotoxicity via modulating
oxidative stress and apoptosis. *Life Sci.* **219**: 238-247 (2019). doi: 10.1016/j.lfs.2019.01.024.
70. Starozhko L.E. Investigation of the immunomodulatory and membrane-active properties of drugs from licorice roots. *Bulletin of Dermatology and Neurology*. **4**:22-25 (1996).
71. Suleimenova R.K., Iztleuov M.K., Sundetov Zh.S., Iztleuov Ye.M. Correction of disorders of the immune status caused by chromium compounds with oil extract from licorice roots. Materials of the International Scientific and Practical Conference. Almaty 46-50.
72. Temirgalieva E.M. Mechanisms of the pharmacological action of the components of licorice root. *Pharmaceutical Bulletin*. 33-34 (2008).
73. Tiwari M, Kakkar P. Plant derived antioxidants - Geraniol and camphene protect rat alveolar macrophages against t-BHP induced oxidative stress. *Toxicol In Vitro.* **23**(2):295-301 (2009). doi: 10.1016/j.tiv.2008.12.014.
74. Tolstikov G.A., Baltina L.A., Shultz E.E., Pokrovsky A.G. Glycyrrhizic acid. *Bioorg. chemistry.* **23**(9): 691-709 (1997).
75. Tolstikov G.A., Myshkin V.A., Baltina L.A. Antidote and antiradical therapy of â-glycyrrhizic acid complexes with pyrimidine derivatives. *Chem.-Pharm. zhurn.* **30**(5): 36-38 (1996).
76. Ueno T, Sata M. [Forefront of therapy for hepatic fibrosis]. *Nihon Shokakibyo Gakkai Zasshi.* **99**(4):691-709 (1997).
77. Utsumomiya T, Kobayashi M, Ito M, Herndon DN, Pollard RB, Suzuki F. Glycyrrhizin restores the impaired IL-12 production in thermally injured mice. *Cytokine.* **14**(1):49-55 (2001). doi: 10.1006/cyto.2001.0847.
78. Verma AR, Vijayakumar M, Rao CV, Mathela CS. In vitro and in vivo antioxidant properties and DNA damage protective activity of green fruit of Ficus glomerata. *Food Chem Toxicol.* **48**(2): 704-9 (2010). doi: 10.1016/j.fct.2009.11.052.
79. Wendell L, Combest P. Herbal Pharmacy: Licorice. https://www.uspharmacist.com/.
80. Yamamoto Y., Majima T., Saiki L., Tani T. Pharmaceutical evaluation of Glycyrrhiza uralensis roots cultivated in eastern Nei-Meng-Gu of China. *Biol Pharm Bull.* **26**(8):1144-9 (2003). doi: 10.1248/bpb.26.1144.
81. Yang R., Pei X., Wang J., Zhang Z., Zhao H., Li Q., Zhao M., Li Y. Protective effect of a marine oligopeptide preparation from chum salmon (Oncorhynchus keta) on radiation-induced immune suppression in mice. *J Sci Food Agric.* **90**(13):2241-8 (2010). doi: 10.1002/jsfa.4077.
82. Yao L., Wang Z., Zhao H, Cheng C., Fu X., Liu J., Yang X. Protective effects of polysaccharides from soybean meal against X-ray radiation induced damage in mouse spleen lymphocytes. *Int J Mol Sci.* **12**(1):8096-104 (2011). doi: 10.3390/ijms12118096.
83. Yazlovitskaya E.M. Radioprotectors and Mitigators: Current Status. *Journal of Bioequivalence & Bioavailability.* **05**(01) (2013). DOI:10.4172/jbb.1000026
84. Zaher N.H., Salem A.A., Ismail A.F. Novel amino acid derivatives bearing thieno [2,3-d] pyrimidine moiety down regulate NF-êB in ã-irradiation mediated rat liver injury. *J Photochem Photobiol B.* **165**:328-339 (2016). doi: 10.1016/j.jphotobiol.2016.10.029.