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Effect of Boric Acid on Oxidative Damage in Immunocompetent Organs under Conditions of Potassium Bichromate and Gamma Radiation Exposure

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The immune system supports antigenic homeostasis in the body and regulates the processes of proliferation and differentiation of cellular components in hemo- and immunopoiesis. Chromium compounds and ionizing radiation lead to the formation of highly reactive free radicals. Sublethal dose of gamma-irradiation is characterized by a 56% decrease in thymus cellularity and a 22% decrease in lymph nodes against the background of a 44% increase in the number of lymphoid cells in the spleen. Under the combined effect of hexavalent chromium and gamma-radiation, a decrease in the number of lymphoid cells is observed. In thymus the cellularity decreases by 70%, in spleen - by 40%, in lymph nodes - by 42% in comparison with control data. Under the influence of boric acid the number of lymphoid cells in thymus significantly increases by 47%, in lymph nodes - by 14% ($p<0.05$) compared to the data of irradiated animals. Boric acid administration weakens the development of oxidative stress, lipid peroxidation decreases, and the activity of antioxidant defense enzymes in immunocompetent cells is increased.

Keywords: Chromium, boron, lipid peroxidation, antioxidant, reactive oxygen species.

Lymphoid cells are very susceptible to radiosensitization[1-3]. The immunodeficiency syndrome appears as damage to lymphopoiesis[4-7] and impaired migration of lymphocytes, loss of their ability to recirculate to a node or other lymphoid unit[8,9]. This is demonstrated by inhibition of cellular factors, depression of the humoral bundle and functional deficiency of the phagocytic component of immunity[10], caused by a complicated set of structural and metabolic disorders. Consequently, prevention, correction and treatment of disorders developing in the body, including in the immune system, remain important.

Hexavalent chromium (CrVI) has a number of negative effects on human health: hepato-, nephro-, immunotoxicity, carcinogenicity, gonado- and embryotoxicity.

Chromium can enter the human body through the skin, mucous membranes, lungs, as well as together with food and water (gastrointestinal tract), but some of its compounds are assimilated easier and faster (this is due to their solubility and valence of the metal in them). Thus, Cr (VI) is assimilated by the body better and faster than Cr (III), which is due to its high solubility at physiological pH values[14].

In particular, we consider in detail the ways of this trace element's entry into the blood. The entry of the metal into the blood is associated with transfer proteins located in the epithelium of the small intestine and carrying out active (energy-consuming) transport of the element. If chromium particles enter the body through the lungs, then when exhaling with a stream of air they get into the oral cavity, from there into the gastrointestinal tract, and the process occurs as described above.

Once in the blood, a part of Cr (VI) binds to erythrocytes, as well as leukocytes and platelets and is reduced to Cr (III), which in turn forms a strong complex with hemoglobin (located on the surface of blood cells) and thus moves around the body. The remaining (unbound) portion of hexavalent chromium is excreted from the body through the kidneys[15].

Cr (III) upon entering the blood binds to the protein transferrin (which is found in the free state in the blood plasma). If Cr (III) enters the body in large quantities, it can bind to the protein albumin, globulin and amino acids in the blood plasma. Thus, the transportation of this element in the blood is carried out. It is important to know that the protein transferrin transports iron in the blood, and the trace element chromium competes with it for binding sites.

Moving through the body in a bound state, chromium accumulates in organs such as the lungs, liver, pancreas, and bone marrow. Chromium has a high affinity for these tissues.

When CrVI enters a cell, it is reduced to metastable pentavalent chromium (Cr(V)) and then to trivalent chromium (Cr(III)), which is accompanied by the generation of reactive oxygen species (ROS) and causes damage to cellular structures, including immunocompetent organs[16]. At the same time, oxidative stress plays the main role in the realization of the damaging effect arising from chromium intoxication. As a result of which, there is a depletion of the immune system with a transition to immunodeficiency[17-21].

In this regard, the search for protective agents is necessary to counteract oxidative damage and increase the capacity of the defense response by activating the immune system.

Boron (B) plays an important role in human and animal bodies[22-25]. Boron has an effect on mineral metabolism, vitamin D absorption, enzyme and hormone production, and it also affects biochemical parameters and ROS[26-29]. Boron has hepatoprotective and antigenotoxic effects[30], antioxidative activity, inhibiting ROS[31-34].

B administration increases the amount of antioxidants in the body (glutathione and its derivatives), thereby limiting oxidative damage to the cell[35]. Boric acid displayed hepatoprotective, antioxidant, anti-inflammatory and immunomodulatory activities in animals[36-37]. Boron supplementation is believed to have immunostimulatory effects, including on T-cell proliferation and increased levels of natural killer cells[38,39]. A number of studies have shown that B reduced levels of inflammatory biomarkers and modulated cellular response in inflammatory processes[40-43], as well as playing a key role as a regulator of immune and inflammatory responses and hematopoiesis[44-47]. According to a number of scientists[48-52], B compounds are found to have a protective effect by modulating oxidative stress indicators.

The effect of B on immune system disorders, on the state of lipid peroxidation and antioxidant system in immunocompetent organs under the influence of Cr(VI) and gamma irradiation has not been studied. Therefore, it was the subject of the current experimental study.

MATERIALS AND METHODS

The experiment was conducted on 70 male Wistar rats weighing 170-190 g. The rats were kept in the vivarium under standard conditions. Lighting was natural, room temperature - in accordance with the approved standards. Nutrition - free availability of food and water.

Animals were kept in standard conditions in the vivarium of the Scientific and Practical Center of the Non-Commercial Joint Stock Company "West Kazakhstan Medical University named after Marat Ospanov" (Aktobe, Republic of Kazakhstan) under natural illumination and maximum normalized temperature and food regime with free access to food and water. The experiment was conducted in accordance with the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Purposes (Strasbourg, 1986). The experimental program was discussed and approved

by the university ethics committee of October 20, 2022, protocol No. 8 (local bioethics committee).

The animals were randomly divided into 5 groups (14 rats in each group) 10 days after they had been acclimatized. The first group was the control group. Animals of the 3rd and 5th groups at the beginning of the experiment received potassium bichromate with drinking water daily for 4 weeks at a dose of 520 mg/L. Animals of the 4th and 5th groups received boric acid in a dose of 400 mg/l.

Four weeks after the start of the experiment, all rats were subjected to gamma irradiation at a sublethal dose (6 Gy, N = 0.54 Gy/min; Teragam radiotherapy unit (manufactured by the Czech Republic, in 2008). The distribution distance from the source to the skin was 70 cm.

Immunological parameters. To study the cells of lymphoid organs of the immune system, suspensions were prepared from thymus, spleen and lymph nodes of the small intestine. The total number of lymphoid cells and organ mass were determined.

Lipid peroxidation and antioxidant status. The content of malondialdehyde (MDA) in tissues of thymus, spleen and intestinal lymph nodes was determined spectrophotometrically according to the Draper method modified by Hadley[53]. Superoxide dismutase (SOD) activity was estimated according to the method of Beauchamp and Fridovich[54]. Catalase (CAT) activity was determined according to the method of Korolyuk[55]. Glutathione peroxidase (GPO) activity was determined according to the method of Flohe and Gunzlcer[56].

Statistical analysis. Statistical data processing was performed using Statistica 10 (StatSoft, Inc., USA) program package.

RESULTS AND DISCUSSIONS

The study of the effect of boric acid on the cellular composition of lymphoid organs showed the following. At sublethal dose of gamma-irradiation (Table 1) there is a decrease of thymus cells by 56%, lymph nodes by 22%, and at the same time the number of lymphoid cells in spleen increases by 44%.

Under the combined effect of CrVI and gamma-radiation there is a decrease in the number of lymphoid cells in all studied immunocompetent organs. In thymus the complex of cell composition decreases by 70%, in spleen - by 40%, in lymph nodes - by 42% in comparison with control data.

Under the influence of boric acid in the irradiated organism the number of lymphoid cells significantly increases in thymus by 47%, in lymph nodes - by 14% ($p<0,05$) compared to the data of animals exposed only to irradiation. The number of cells in the spleen is at the level of the control group data. Prophylactic administration of boric acid under combined exposure to CRVI and ã-irradiation causes an increase in the composition of thymus cells by 75%, spleen by 87%, lymph nodes by 22% compared to the data of positive control animals (CRVI and ã-irradiation).

The effect of CrVI and ã-irradiation on lipid peroxidation and antioxidant status in immunocompetent organs was evaluated, as well as the protective effect of boric acid under these exposure conditions.

Under the action of a sublethal dose of gamma-irradiation there was observed an increase of MDA in lymph nodes by 69%, in spleen and thymus tissues by 40 and 57%, respectively, compared to the control. SOD activity was decreased in lymph nodes, spleen and thymus tissues by 35, 27 and 22%, respectively. The activity of catalase, respectively, by 39, 47 and 53%, the activity of HPO - by 17, 37 and 20%, respectively (Table 2) compared to the data of animals of the control group.

Prophylactic administration of boric acid under conditions of isolated exposure to gamma-irradiation was accompanied by reduction of MDA content in lymph nodes by 26%, in spleen and thymus tissues - by 19 and 25%. Accordingly, the activity of SOD, GPO and CAT in lymph nodes increased by 41, 31 and 43% respectively, in spleen tissues - by 19, 64 and 200% respectively, in thymus tissues - by 21, 51 and 100% compared to the data of positive control (gamma-irradiation).

The combined effect of CrVI and gamma-irradiation resulted in the increase of MDA level in lymph nodes, spleen and thymus tissues by 169 and 122, 157%, respectively.

Antioxidant system enzymes - SOD activity in lymph nodes, in spleen and thymus tissues - by 46, 36 and 40% respectively, HPO activity - by 27, 45 and 32% respectively, CAT - by 55, 64 and 62% compared to control.

Table 1. Effects of boric acid on the lymphoid organs (cellularity) under conditions of isolated and combined exposure to potassium bichromate and gamma radiation

Cellularity(*10^6/gr)	Control	IRR	Cr+IRR	B+IRR	B+Cr+IRR
Thymus	1650±157	720±75*	503±87*	1056±133*	880±90*$_0$
Spleen	363±46	521±61*	213±33$_0$	330±48$_0$	403±54$_0$
Lymph nodes	937±120	727±93*	543±75*	831±93*	660±77$_0$

Note: * - p<0.05; compared with the data of positive control groups among themselves - 0-p<0.05;
IRR - gamma radiation; Cr+IRR – potassium bichromate + gamma radiation; B - is boric acid.

Table 2. The effect of boric acid on the level of malondialdehyde and the activity of enzymes of the antioxidant system in immunocompetent organs with isolated and combined effects of bichromate and gamma irradiation

	Object of study	Control	IRR	Cr+IRR	B+IRR	B+(Cr+IRR)
MDA, nmol/ml	Lymph nodes	16±1.8	27±2.5*	43±4.3*	20±1.8*	27±2.4*
	Spleen	23±3.0	32.2±5.1*	51.1±8.4$_0$	26±2.7$_0$	33±5.3*$_0$
	Thymus	21±2.12	36±4.8*	54±9.0*	27±2.2*$_0$	39±5.4*$_0$
SOD, unit/ml	Lymph nodes	26±3.3	17±1.8*	14±1.3*	24±2.1$_0$	21±2.7*$_0$
	Spleen	66±9.0	48±5.4$_*$	44±5.2$_*$	57±9.0*$_0$	62±8.1$_0$
	Thymus	45±5.0	33±3.0$_*$	27±2.5*	40±3.9$_0$	36±4.0*
GPO, unit/ml	Lymph nodes	247±38	206±45$_*$	180±30$_*$	270±43$_0$	23±40$_0$
	Spleen	275±35	172±36$_*$	151±30$_*$	282±50$_0$	186±33*$_0$
	Thymus	133±26	106±21$_*$	90±18$_*$	166±36^0	128±33$_0$
CAT, mol/s	Lymph nodes	49±8.1	30±6.6$_*$	22±4.0*	43±7.2$_0$	33±6.6*$_0$
	Spleen	33±3.9	16±3.6*	12±30*	48±9.9*$_0$	27±6.6$_0$
	Thymus	52±8.4	25±5.2*	20±3.6*	50±7.0$_0$	40±5.4*$_0$

Note: * – p<0.05; o - p < 0.05 compared with the data of the positive group; IRR - gamma irradiation; Cr+IRR – potassium bichromate + gamma irradiation

Administration of group B compounds under conditions of combined exposure to Cr VI and gamma-irradiation led to a decrease in MDA content in lymph nodes by 37%, in spleen tissues - by 35%, in thymus tissues - by 28%. The activity of enzymes increased. SOD activity in spleen, thymus and lymph node tissues by 41, 33 and 50%, respectively; catalase activity by 125, 100 and 50%, respectively; VI and ICR.

Under the influence of CRVI and gamma irradiation, LPO and AOS disorders were more pronounced (p<0.05). SOD activity in spleen tissues (p>0.05), HPO activity in lymph nodes (p>0.05), in spleen and thymus tissues (p>0.05) were the exceptions (Table 2) compared to the data of gamma-irradiated animals.

In response to extreme radiation exposure, various pathological processes develop, affecting the immune system, which is very sensitive to the action of ionizing radiation[57] and heavy metals[58,59]. Ionizing radiation and chromium cause destruction of lymphoid tissue[60].

Considering the diverse functions of B compounds as regulators of immune, inflammatory reactions and hematopoiesis[61], we hypothesized that the positive effect of boric acid may be useful for the prevention of immune system disorders. Especially in the case of oxidative damage of immunocompetent organs under the combined effect of CrVI and gamma radiation.

Another mechanism of action of boric acid may be the antioxidant potential of boron compounds. Boron may counteract the inhibitory effect of oxidative stress on lymphocyte proliferation. In our previous studies[62-64], it was found that boric acid at a low dose (400 mg/L), sodium tetraborate at a dose of 22.5 mg/kg body weight when co-administered with potassium

bichromate (700 mg/L) exhibited antioxidant effects and reduced damage to immunocompetent organs, providing an immunoprotective effect.

Application of boric acid in a dose of 400 mg/l daily for 28 days reduces the amount of MDA in lymph nodes, thymus and spleen tissues by 26, 25 and 19%, respectively, as well as by 37, 28 and 35% compared to the data of animals of the corresponding groups of positive control. The activity of antioxidant defense enzymes SOD, GPO and CAT in the studied immunocompetent organs, respectively, significantly ($p<0.05$) increased both at isolated and combined exposure compared to the data of positive control animals (irradiation, CRVI + irradiation). Under the same experimental conditions, boric acid causes an increase in cellularity of lymph nodes, in spleen and thymus tissues. Apparently, B compounds can promote lymphocyte multiplication by increasing the antioxidant potential of cells.

CONCLUSION

The combined and isolated effect of Cr and gamma-irradiation leads to activation of free-radical oxidation with a decrease in the activity of the antioxidant system in lymphoid organs. This contributes to changes in immunologic and biochemical indices, which leads to depletion of cells in the organs of immunogenesis and development of immunologic suppression. Boric acid administration attenuates the development of oxidative stress, lipid peroxidation decreases, and the activity of antioxidant defense enzymes in immunocompetent cells increases. Boric acid modulates the entire immune response, playing a key role in the regulation of immune and inflammatory reactions.

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Conflict of interest

There is no conflict of interest.

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REFERENCES

1. Æåòïèñáàåâ Á.À., Óðàçàëèíà Í.Ì., Êàíàôèíà Ì.Ì., Ðàñïîïèíà Í.È. Ôèòîïðåïàðàòû è èììóíàÿ ñèñòåìà îáëó÷åííîãî îðãàíèçìà. Àêòóàëüíûå âîïðîñû ïàòîôèçèîëîãèè è ìåäèöèíû. Ìàòåðèàëû Ìåæäóíàðîäíîé íàó÷íî-ïðàêòè÷åñêîé êîíôåðåíöèè. Àëìàòû: 2008; 157-167.
2. MagalhÓes D.A., Silveira E.L., Junta C.M. Promiscuous gene expression in the thymus: The root of central tolerance. Clinical and Developmental Immunol. 2006; 2 (13); 81-99.
3. Malecka A., Wang Q., Shah S. Stromal fibroblasts support dendritic cells to maintain IL-23. The 17 responses after exposure to ionizing radiation. J.Leukoc.Biol. 2016; 1015-1474.
4. Oradovskaya I.V., Radzivil T.T. Influence of Professional contact with Plutonium-239 on Indicator of the Immune status of the personnel at Siberian Chemical Plant Radiats Biol.Radioecol. Journal: 2015; 55(6): 565-583.
5. Guida M.S., Abd El-Aal A., Kafafy Y. Thymoquinone Rescues T lymphocytes from Gamma irradiation induced Apoptosis and Exhaustion by Modulating Pro-Inflammatory Cytokine Levels and PD-1, Bax, and Bcl-2 Signaling. Cell Physiol. Biochem. 2016; 38(2):786-800.
6. Morgan W.F. Radiation – induced genomic instability. Health Phys. 2011; 100(3): 280-281.
7. Ãóëèê Å.Ñ., Êîñòåøà Í.ß., Áîðèëî Ã.À. Âëèÿíèå õèòàáèñà è åãî êîìïîíåíòîâ íà ñòðóêòóðíî-ôóíêöèîíàëüíîå ñîñòîÿíèå òîíêîãî êèøå÷íèêà è êðîâåòâîðåíèÿ îáëó÷åííûõ êðûñ. Âåñòíèê Òîìñêîãî ãîñóäàðñòâåííîãî óíèâåðñèòåòà. Áèîëîãèÿ. 2012; 3 (19): 146-159
8. Willams J.P., McBride W.H. After the bomb drops: A new look at radiation-induced multiple organ dysfunction syndrome. International Journal of Radiation Biology 2011; 87(8):851-868.
9. Àëåêåíîâà À.À., Êàáäîëëàåâà Ñ.Ç., Æàðìàõàíîâà Ã.Ì., Èëüäåðáàåâà Ã.Î. Èçìåíåíèÿ â èììóííîé è àíòèîêñèäàíòíîé ñèñòåìå ïðè äåéñòâèè âûñîêîé äîçû ãàììà-èçëó÷åíèÿ â îòäàëåííîì ïåðèîäå. Ñåðèÿ êîíôåðåíöèé ÇÊÌÓ èìåíè Ìàðàòà Îñïàíîâà, 2019; 8: 68-74
10. Ìàäèåâà Ì.Ð., Æåòïèñáàåâ Á.À., Óçáåêîâà Ñ.Å., Æåòïèñáàåâà Õ.Ñ., Ñàéäàõìåòîâà À.Ñ., Òîêåøåâà Ã.Ì., Ðàêûìæàíîâà Ñ.Î. Íåñïåöèôè÷åñêàÿ ôàãîöèòàðíàÿ ðåçèñòåíòíîñòü â îòäàëåííîì ïåðèîäå ïîñëå âîçäåéñòâèÿ ðàçëè÷íûõ äîç ãàììà èçëó÷åíèÿ. Àñòàíà ìåäèöèíàëûê æóðíàëû, 2010; 2(60): 162-165
11. Jagetia G.C., Venkatesha V.A. Mangiferin protects human peripheral blood lymphocytes

against radiation-induced DNA strand breaks: A fluorescence analysis of DNA unwinding assay. Nutr.Res. 2006; 26: 303-11

12. Ozasa K., Shimizu Y., Suyama A., Kasagi F., Soda M., Grant E.Y. et.al. Studies of the mortality of atomic bomb survivors. Reprot 14, 1950-2003. An overview of cancer and noncancer diseases. Radiat.Res.2012; 177: 229-43.
13. O'Brien T.J., Ceryak Sand S.R.Patierno. Complexities of chromium carcinogenesis: role of cellular response, repair and recovery mechanism. Mutat. Res. 2003; 533: 3-36.
14. Ìàìûðáàåâ À.À. Òîêñèêîëîãèÿ õðîìà è åãî ñîåäèíåíèé. Àêòîáå, 2012: 284.
15. Æåòïèñáàåâ Á.À., Íóðìàãåâà Ã.Ò., Àð"ûíáåêîâà À.Ñ., Èáðàãèìîâà Ë.À. Ôèòîêîððåöèÿ íàíåíà ïóðèíîâûõ íóêëåîòèäîâ â ïå÷åíè è íàäïî÷å÷íèêàõ ïðè ñî÷åòàííîì äåéñòâèè ñòðåññîãåííûõôàêòîðîâ. Ñåðèè êîíôåðåíöèé ÇÊÌÓ èìåíè Ìàðàòà Îñïàíîâà 2019; VIII: 47-52.
16. Èçòëåóîâ Ì.Ê., Ãîìåîñòàç è õðîìîâàÿ ïàòîëîãèÿ. Ìíîãðàôèÿ. - Àêòîáå, 2003. - 213.
17. Ñóëåéìåíîâà Ð.Ê., Èçòëåóîâ Ì.Ê., Ñóíäóêîâ Æ.Ñ., Èçòëåóîâ Å.Ì. Êîððåêöèÿ ìàñëÿíûì ýêñòðàêòîì èç êîðíåé ñîëîâêè íàðóøåíèé èììóíîãî ñòàòóñà, âûçâàâøèõ ñîâäëíåíèÿìè õðîìà. Ìåæäóíàðîäíàÿ íàó÷íî – ïðàêòè÷åñêàÿ êîíôåðåíöèÿ «Àêòóàëüíûå âîïðîñû ïàòîôèçèîëîãèè è ìåäèöèíû». Àëìàòû, 2008; - 46-50.
18. Èçòëåóîâ Ì.Ê., Èçòëåóîâ Å.Ì. Õðîì ìåí áîð ›îñûëûñòàðûíü£ á³ðëåñêåí Ùñåð³íåí èíäóêöèÿëàí"àí ðåïðîäóêöèîí³ê ôóíêöèÿ á±çûëûñòàðûí áà"àëàó æÙíå êîððåêöèÿëàó. Øã³ñòåìåë³ê í±ñ›àóëàð. À›òéáå: «Ìàðàò Îñïàíîâ àòûíãà"û ÁšÌÓ» ÊîÀš, 2022; 345.
19. Dai L., Xu W., Li H., Frank J.A., He C., Zhang Z., Chen G., 2017 Effects of hexavalent chromium on mouse splenic T lymphocytes. Toxicology in Vitro.
20. Karaulov A.V., Renieri E.A., Smolyagin A.I., Mikhaylova I.V., Stadnikov A.A., Begun D.N. Long-term effects of chromium on morphological and immunological parameters of Wistar rats. Food and Chemical Toxicology; 2019: 133. 154-167
21. Nielson F.H. The Nutritional Importance and Pharmacological Potential of Boron for Higher Animals and Human. Boron in Plant and Animal Nutrition. 2002; 37-49.
22. Cheng J.Y., Peng K.M., Jin E.H., Lui Y. Zhand N., Song H., Liu H., Tang Z. Effect of additional boron on tibias of African ost;xch chicks. Biol 1 race Elem. Res; 2011; 144(1 -3): 538-549.
23. Ying X.Z., Cheng S.W., Wang W., Lin Z.Q., Chen Q.Y., Zhang W., Kou D.Q., Shen Y., Cheng X.J., Rompis F.A., Peng L., Zhu Lu C. Effect of boron on osteogenic differentiation of human bone marrow stromal cells. Biological Trace, Element Research. 2011; 144(1-3): 306-315.
24. Hunt C.D. Biochemical effects of physiological amounts of dietary boron. The Journal of Trace Elements in Experimental Medicine. 1996; 9:185-213.
25. Armstrong T.A., Spears J.W., Lloyd K.E. Inflammatory response, growth, and thyroid hormone concentrations are affected by long-term boron supplementation in gilts. J AnimSci. 2001; 79(6): 1549-56.
26. Ince S., Kucukkurt I., Demirel H.H., Acaroz D.A., Akbel E., Cigerci I.H. Protective effects of boron on cyclophosphamide induced lipid peroxidation and genotoxicity rats. Chemosphere. 2014; 108:197-204.
27. Acaroz U., Ince S., Arslan-Acaroz D., Gurler Z., Kucukkurt I., Demirel H. Htiseyin A.N., Halil O., Varol N., Zhu K. The ameliorative effects of boron against acrylamide-induced oxidative stress, inflammatory response and metabolic changes in rats. Food and chemical toxicology. 2018; 118:745-752.
28. Pawa S., Ali S. Boron ameliorates fulminant hepatic failure by counteracting the changes associated with oxidative stress. Chem. Biol. Interact; 2006; 160: 89-98.
29. Coban F.K., Liman R., Cigerci I.H., Hazman O., Sinan I., Bozkurt M.F. The antioxidant effects of boron on oxidative stress and DNA damage in diabetic rats. Fresenius Environmental Bulletin 24: 4059-4066.
30. Kakarla P., Vadluri G., Reddy K.S. Response of hepatic antioxidant system to exercise training in aging female rat. J. Exp. Zool. A Comp. Exp. Biol. 2005; 303(3):203-208.
31. Knyshova V.V. Effect of boron-coniaining mineral waters on the lipid peroxidation status and antioxidant defense factors in experimental gastroduodenitis. Vopr Kurortol Fizioter Lech Fiz Kult. 2002, 2: 34-36.
32. Ince S., Kucukkurt I., Gigerci I.H., Fidan A.F., Ergavus A. The effects of dietary boric acid and borax supplementation on lipid peroxidation antioxidant activity and DNA damage in rats. J. of Trace Elements in Medicine and Biology. 2010; 24(3): 161-164.
33. Hunt C.D. Regulation of enzymatic activity: one possible role of dietary boron in higher animals and humans. Biol Trace Elem Res. 1998; 66(l-3):205-25.
34. Bolt H.M., Ba°aran N., Duydu Y. Effects of boron compounds on human reproduction. Archives of Toxicology 2020; 94(3): 717-724.
35. Gendiz M., Hematoprotective effect of boron

on cyclopkosphamide toxicity in rats. Cell Mol. Biol. 2018, 64(5): 65-72
36. Ozdemir H., Yaren B., Oto G. Effect of Dietary boron on learning and behavior in rats administered with boric acid. 2019, 65(1): 65-72
37. Naghi M.R., Mofid M., Asgari A.R., Hedayati M., Daneshpour M. Comparative effects of daily and weekly boron supplementation on plasma steroid hormones and proinflammatory cytokines. J.Trace Elem. Med. Biol. 2011, 25(1): 54-58
38. Rogoveanu O.C., Mogoºanu, G.D., Bejenaru C., Bejenaru L.E., Croitore O., Neamtu I. et. al. Effects of calcium fruetoborate on levels of c- reactive protein, total cholesterol, low-density lipoprotein, triglycerides, IL-lb, IL-6, and MCP-1: a double-blind, placebo-controlled clinical study. Biol.Trall Elem. Res. 2015; 63(1): 124-131
39. Armstrong T.A, Spears J.W. Effect of boron supplementation of pig diets on the production of tumor necrosis factor-alpha and interferon-gamma. J. Anim. Sei 2003; 81(10):2552-2561
40. Routray I., Ali S. (2016) Boron Induces Lymphocyte the Proliferation and Modulates the Priming Effects lipopolysaccharide on Macrophages Plos ONE 11(3): e0150607.
41. Turkez H. Effect of boric acid and borax on titanium dioxide genotoxicity. J. Appl. Toxicol. 2008; 28(5): 658-664
42. Turkez H., Geyikoglu F. and Çolak S. The protective effect of boric acid on aluminium - indiced hepatotoxicity and genotoxicitv in rats. Turkish Journal of Biology. 2011; 35:293-301.
43. Çolak S., Geyikoglu F., Keles O.N., Turkez H., Topal A., Unal B. The neuroprotective role of boric acid on aluminum chloride-induced neurotoxicity. Toxicol Ind Health. 2011; 27(8):700-10.
44. Iztleuov Y.M., Kubenova N.N., Ismailova I.V. and Iztleuov M.K. Protective Action of Sodium Tetraborate on Chrom-induced Hepato- and Genotoxicity in Rats. Biomedical & Pharmacology Journal. 2017; 10(3):1239-1247.
45. Iztleuov Y., Abilov T., Zhanabayeva G., Ismailoval. and Iztleuov M. Protective Effect of Sodium Tetraborate on Chromium-induced Brain Damage in Rats. Biomedical & Pharmacology Journal. 2018; 11(1): 227-236.
46. Èçòëåóîâ Ì.Ê., Èçòëåóîâ Å.Ì., Òóðãàíáàåâà À.Ó., Ñàìáàåâà Ñ.Ñ., Ìàäèðàí Æ.Ø., Èçòëåóîâà Ã.Ì. Âëèÿíèå ñîåäèíåíèé áîðà íà ððîì-èíäóöèðîâàííûå îêèñëèòåëüíûå ïîðàæåíèÿ â èììóíîìîäåíèòîõ îðãàíàõ êðûñ. West Kazakhstan Medical Journal. 2019; 61(4): 229-236
47. Hu Q., Li S., Qiao E., Tang Z., Lin G., Gu Y., Effects of Boron jn Structure and Antioxidative of Structure and Rats. Biol. Irace Elem. Res. 2014; 158:73-80.
48. Mancini G., Vaerman J.P., Carbonara A.0. Heremans J.F. A single radial diffusion method for the immunological quantitation of proteins. (Peetere H ed) Protides of Biological fluids. - Amsterdam. The Netherlands: Elsever, 1964.- 370-373.
49. Êîñò Å.À., Ñòåíêî È.Â. Èññëåäîâàíèÿ ôàãîöèòîçà ïî êëåíè÷åñêèì è ëàáîðàòîðíûì ìåòîäàì èññëåäîâàíèÿ. Ìîñêâà, 1968; 78-80
50. Íàãîåâ Á.Ñ., Øóáè÷ Ì.Ã. Çíà÷åíèÿ òåñòà âîññòàíîâëåíèÿ íèòðîñèíåãî òåòðàçîëèëü äëÿ èçó÷åíèÿ ôóíêöèîíàëüíîé âêòèâíîñòè ëåéêîöèòîâ. Ëàáîðàòîðíîå äåëî. 1981; 4: 195-198
51. Draper H.H., Hadley M. Malon dialdehyde determination as index of lipid peroxidation. Methods Ezymol; 1990; 186: 421-431.
52. Koroluk M.A., Ivanova L.I., Mayorova I.G., Tokarev V.E. Method for the determination of catalase activity. Laboratory work. 1988: 5:16-18
53. Beauchamp C., Fridovich I. Superoxide disinutase: improved assays and an assay applicable to acrylamide gels. Anal. Biochem.,1971: 44(1): 276-287.
54. Flohe L., Gunzler W.A. Assays of glutathione peroxidase Methods in Enzymology. 1984; 105:114-121
55. Dainiak N. Hematologic consequences of exposure to ionizing radiation. Exp. Hematol 2002; 30: 513-528.
56. Salah - Abbes, J. Ben, Abbès, S. Zohra H, Oueslati R. 2015, Tunisian radish (Raphanus sativus) extract prevents cadmium-induced Immutoxic and biochemical alterations in rats.
57. ßðìîíåíêî Ñ.Ï., Âàéñìí À.À. Ðàäèîáèîëîãèÿ ÷åëîâåêà è æèâîòíûõ: Ó÷.ïîñîáèå. Ìîñêâà: Âûñøàÿ øêîëà, 2004.-549ñ.
58. Marat Iztleuov, Marat Teleuov, Yerbolat Iztleuov, Samat Saparbaev, Alma Yelubayeva, Gulmira Yemzharova, Sanimgul Sambayeva, Aigul Turganbayeva and Zhanat Umirzakova. Influence of the Herbal Preparation "Licorice Oil" on the State of Hematopoiesis in Rats lionizing lrradiation. Biomedical Pharmocology Journal, June 2021; 14(2):869-879.
59. Dranoff G. 2004. Cytokines in cancer pathogenesis and cancer therapy. Nat. Rev Cancer
60. Cangemi S., Gofita E., Costa C., Teodoro M., Briguglio G., Nikitovic D., Tznararis G., Tsatsakis A.M., Wilrs M.F., Spendidos D.A., Fenga C. 2016. Occupational and environmental exposure to pesticides and cytokine pathways in chronic diseases (Review). Int. I Mol. Med.
61. Ì.Ê. Èçòëåóîâ, Ê.Ì. Êèáàòàåâ, Ò.Ñ. Àáèêîâ, Å.Ì. Èçòëåóîâ, Æ.Ø. Ìàäèðàí. Ãåíîòîêñè÷íîñòü

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62. M. Iztleuov, Ye. Iztleuov, S. Saparbayev, A. Temirbayeva, R. Medeuova, Z. Aleuova, I. Ismailova, N. Imanbayev. Effect of Burdock Root Oil on Oxidative Stress Induced By Isolated and Combined Use of Gamma Radiation and Hexavalent Chromium. Biomedical and Pharmacology Journal. 15(1), 421-432. March 2022.
63. Di Maggio, I.M., Minafica L., Cammarota F.P., Messa C., Gilardi M.C., Bravata V. Portrait of inflammatory response to ionizing radiation treatment. J. Inflammation, 2015; 12(1):14-18.
64. Jagtap SV. Evaluation of CD4+ T-cells and CD8+ T-cells in triple-negative invasive breast cancer. Indian J Pathol Microbiol. 2028; 61:477-488: