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EVALUATION OF ANTIOXIDATIVE POTENTIAL OF LICORICE ROOT EXTRACT IN RATS DURING LONG-TERM INHALATION OF SMALL AND LARGE DOSES OF URANIUM ORE DUST

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Abstract

Objectives. *This work is aimed to evaluate the antioxidative potential of licorice root extraction antioxidative protection system during long exposure of animals by uranium ore dust in small and large dozes.* **Materials and methods.** *In healthy outbred male rats in different terms of inhalation of uranium ore dust (3-120 days) by different intensity (5, 10 and 50 MPC) the activity of superoxide dismutase was assessed in their lung tissue and blood serum with and without oral administration of the licorice root extract in 100 mg/kg.* **Results and discussion.** *The action of the licorice root extract on rats during their inhalation of different doses of the uranium ore dust on the activity of superoxide dismutase had positive dose and time dependence. Licorice root extract has a positive impact on modifying disorders of oxidative metabolism. However, its efficiency depends on the depth of the disorders and duration of the radiotoxic action of the uranium ore dust. The most effective correction was found in rats which inhaled the uranium ore dust equal to 5 MPC doze, with the almost 3-fold increase of the superoxide dismutase's activity. During massive exposure of large doses of uranium ore dust, the licorice root extract restored the superoxide dismutase activity to 60% in 30 seconds. Subsequent decreases were found in this positive effect.* **Conclusion.** *Oral administration of the water extract of licorice root in a dose of 100 mg/kg raises the activity of superoxide dismutase. Change in superoxide dismutase activity was found to depend on the duration and the depth of radiotoxic effect of the uranium ore dust.*

Keywords: *uranium ore dust, lipid peroxidation processes, lung tissue, serum, malondialdehyde, rats, licorice root extract, superoxide dismutase.*

Introduction

At present, the development and application of effective radioprotective means is extremely urgent. Among directions in this sphere is the study of radioprotective and immunomodulatory properties of herbal substances with the purpose to increase immunoresponsiveness of the body when exposed to ionizing radiation (Arora R, et al., 2005; Dutta A, et al., 2012; Khan AA, et al., 2016).

Many herbs revealed radioprotective properties (Arora R et al, 2005; Hosseinimehr SJ, 2007; Szejk M, et al, 2016; Kim W. et al, 2017). In this respect the study of pharmacological activity of licorice root is of significant interest. The licorice root (*Radix glycyrrhizae*) contains more than 20 biologically active substances and has versatile medical effects on a body (Akao T, 1999; Akao T, 2000; Fukuchi K, et al, 2016; Hejazi II, et al, 2017). There are currently unexplored biologically active substances still to be discovered. The glycyrrhetic acid of the licorice root is a cortisone synergist and has powerful anti-inflammatory effect (Dvinskaya CA., et al, 2003; Dhingra D., et al, 2004; Fogelman Y., et al., 2016; Fukuchi K., et al, 2016). Like hydrocortisone, it has rendered positive effects on the resolution of tumors in several studies. The presence of certain antileukemic effects of both glycyrrhetic acid and its derivatives has been established. It has been shown that glycyrrhetic and glycyrrhizic acids and their derivatives have anti-inflammatory and mineralocorticoid effects (Zaretskiy BV, 1996).

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Interest and studies of licorice root has shown that licorice is among the most medicinally powerful plants known in the world. It has even supplanted previous miracle plants ginseng (*Panax ginseng*) and gold root (*Rhodiolarosea*) (Li IA, et al, 2003). In ancient times, the licorice root extract was used in the treatment of many diseases and in complexes with other medicines (Zhao S et al, 1991; Zhou MY, 2001; Zhang W et al, 2004; Chang Y-T, et al, 2009). In a number of studies, radioprotective properties of this extract were investigated, but in all of these studies the licorice root was found within Chinese formulas or just as separate flavonoids of licorice (Kim S-H et al, 2002; Becker SA, 2001; Jo EH, et al, 2004). Despite the wide spectrum of the literature on the use of medicines synthesized from licorice root, there were no studies which investigated the effect of licorice root extract on functions of the respiratory system or as an antioxidant in the case of uranium intoxication (Tajiev AC, et al, 2000; Zhou MY et al, 2001; Liu Z-L et al, 2002).

The major element of the antioxidative protective system of the body and its biomarker is superoxide dismutase (SOD) (Gusev VA, et al, 1980; Hassan HM, 1988; Scott MD, et al, 1989; Cadenas E, 1989; Zhuan B, et al, 2017; Gulati S, et al, 2017). SOD is related to a class of enzymes – metalloproteins. SOD catalyzes the dismutation of superoxide radicals into oxygen and hydrogen peroxide. A metal cofactor associated with the enzyme has been used to distinguish three types of the enzyme: containing one atom of copper or zinc, and manganese and iron. Prokaryotes contain SOD with manganese (MnSOD), iron (FeSOD) or both metals (McCord JM, et al, 1977).

In the connection with stated above, *the purpose of this study* is to assess the antioxidative effects of the extract of licorice root in rats during long exposure of them to small and large doses the uranium dust.

MATERIALS AND METHODS

Material and protocol. The experimental part is carried out on 228 white male rats with initial weight 140-180 g divided into 8 groups:

№ 1 - group of the initial control - 24 rats

№ 2 - group of the control for other 6 experimental groups - 72 rats

№ 3 - experimental group received UOD dose of 5 maximum permissible concentrations (MPC) (10.775 mg/m^3) by inhalation – 36 rats

№ 4 - UOD dose of 10 MPC by inhalation (20.55 mg/m^3) – 36 rats

№ 5 - UOD dose of 50 MPC by inhalation (107.75 mg/m^3) – 36 rats

№ 6 - UOD dose of 50 MPC by inhalation (107.75 mg/m^3) and simultaneous treatment with licorice root extract - 36 animals

№ 7 - UOD dose of 5 MPC (10.775 mg/m^3) and treatment with licorice root extract for 30 days - 36 animals

№ 8 - UOD dose of 10 MPC (20.55 mg/m^3) and treatment with licorice root extract for 30 days - 36 animals.

Inhalation exposure of animals by the UOD was carried out in special primer chambers UIP-1. Their design provides an easy approach to force air directly into respiratory airways. The dust concentration in primer chamber air was kept homogeneous and constant. Uranium dust from the Stepnogorsk mining and chemical plant was applied to the primer. The chemical structure of the dust is described in the following percentages: U – 0.332; Mo– 0.082; Zn – 0.020; Fe– 4.27; SiO_2– 40.60; Al– 2.44; As – 0.006; Mn– 0.14. The total α-radioactivity of the dust was 202 Bq/g. The MPC of the dust for a working zone air is 2 mg/m^3.

The experiments were carried out for 4 hours each day in a 5 day work week, continuously for 120 days at doses 5 and 10 MPC, and within 60 days at the dose of 50 MPC. A separate group of animals (№6) was exposed to the UOD in the dose of 50 MPC for a week prior to the beginning the experiment, and then during the study were treated with 2 ml of the licorice root extract (LRE) per os (calculated on the base of 100 мг/kg of weight). To study modifying effect of the LRE on postradiational changes of antioxidative protection system of rats exposed by small doses of the UOD (5 and 10 MPC), animals after termination of the UOD primer were administered per os by the LRE during 30 days. The total study length was 150 days. In all cases, the control group of animals was investigated according to the research terms.

The primer conditions and duration of the research were conducted in accordance to the international recommendations (ICLAS, 1978; WHO, 1981; Lanimage, 1993).

Bioethical considerations. The design and protocol of experimental studies were approved by the

local bioethical committee of the JSC "Astana Medical University".

Measurement of SOD in lung tissue. The SOD concentration was measured by the spectrophotometric method of Chevari C, Chaba I and Sekey Y (1975) based on the restoration of nitrotetrazolium by superoxide radicals, which are formed in a reaction between phenazinemethosulfate and the restored form of nicotinamide adenine dinucleotide (NAD*H). The formation of nitroformazane, the product of restoration of nitrotetrazolium, is blocked by the SOD contained in this probe.

The SOD is defined in 1 ml of homogenate of the lung tissue and mixed intensively and centrifuged during 30 min at 4000-5000 rev/min. Then 0.5 ml of a mix of EDTA and 0.1 ml of NAD*H solution, previously dissolved in 100 ml tris-EDTA-buffer, were added to 0.1 ml of the formed supernatant.

Statistical Analysis. Comparisons between experimental groups and relevant controls were performed by Student's t-test. Significance of differences was tested using ANOVA, with $P < 0.05$ as the limit of significance.

Results

The changes in SOD activity by percent (%) in rats' lung tissue and blood serum during inhalation of the UOD in doses 5, 10 and 50 MPC with and without treatment by licorice root extract. The study of the SOD activity in lung and blood serum (table 1) shows that the 30s day of UOD inhalation results in an average decrease of 2x in SOD activity. Beginning with the 2nd month of the primer treatment the activity of SOD in the lung tissue had a slight increase but remained below that found in the control group on 30.7 %. In the blood serum SOD shows an almost 4x loss in activity. By the end of 3rd month, SOD activity in lung tissue was oppressed by 2.2x, and in the blood serum by 3.6x. By the day 120, the reduction of the enzyme's activity was 5.4x in the lung and in 6.3x in blood serum.

Exposure to the UOD in the dose of 10 MPC. By the end of month 1 of the primer treatment, the activity of SOD in investigated tissues was decreased by an average of one half. By the end of month 2, the enzyme's activity was decreased in 2.6x in the lung tissue and in the blood serum it decreased in 6.1x. By day 91 of the primer treatment, SOD's activity slightly increased in observed tissues but did not reach above 50% of normal activity. By the end of the month 4 the SOD continued to lose activity in the lung tissue, whereas in the blood it remained within the levels noticed by month 3.

Exposure to the UOD in the doze of 50 MPC. By the day 3 SOD's activity in lung tissue did not significantly changed, but in the blood serum it had decreased slightly by approximately 7 %. On days 7, 30 and 60 the enzyme's activity in the lung tissue was gradually reduced to 27.9-48.5-44.5 % accordingly, and in the blood serum to 3.7-42.3-55 % accordingly.

Thus, in the group of rats that were exposed to UOD in the dose of 5 MPC, the maximum of decrease of the SOD's activity was found by day 120, the end of the experiment. In the group of animals exposed to the UOD in the dose of 10 MPC, the maximum decrease in SOD activity in the lungs was also found at the end of the experiment. However, in the blood serum the maximum decrease in SOD activity was found in month 2 of the experiment with a subsequent small restoration of the SOD's activity. In the third group of rats exposed to 50 MPC of the UOD, the minimum of SOD's activity in lungs was observed at the end of the first month. The lowest SOD activity in blood serum was observed at the end of the 4th month.

The efficiency of action of the licorice root extract differed by exposure to UOD. At day 150, in rats inhaling the UOD in the dose of 5 MPC, the oral administration of the LRE increased the SOD's activity almost 3 fold in lung tissues and 5x in the blood serum. In animals inhaling the UOD in the dose of 10 MPC, the LRE increased the enzyme's activity more than in 1.5x in the lung tissue and in 2.2x in the blood serum. The administration of the LRE for rats inhaling the UOD in the dose of 50 MPC increased SOD's activity in the lung tissue up to normal levels on days 3 and 7 of the study. On days 30 and 60, when the SOD's activity was maximally suppressed, the LRE raised the enzyme's activity to 60% and 26% in the lung tissues and 63% and 117% in the blood serum. However, even in these conditions the SOD parameters in the lung tissues were not restored and were below the norms by approximately 17.6% and 30 % accordingly.

Discussion

TABLE 1.

The changes in superoxide dismutase activity by percent (%) in rats' lung (in L rows) and blood serum (in H rows) during inhalation of the UOD with and without treatment by licorice root extractt

Group of rats	Dose of UOD		Experiment terms (days)						
			3	7	30	60	90	120	150
Intact rats (Norm)		***L***				62.5±2.5			
		H				71.14±6.2			
Intact rats (control group)		***L***	66.4±2.5	61.1±21.9	66.4±2.9	60.2±2.1	66.4±2.9	60.1±2.3	
		H	69.8±5.8	70.6±6.1	70.8±5.8	71.1±6.2	71.8±5.4	70.9±6.2	
Exposed to UOD (experiment)	5 MPC	***L***			33.7±0.9	41.7±1.4	27.1±5.4	11.2±0.8*	
		H			33.8±1.7*	19.8±0.6*	19.9±0.1*	11.3±0.9*	
	10 MPC	***L***			33.8±2.9	23.9±0.6	28.3±1.0	17.3±5.8	
		H			31.8±2.0*	11.6±1.1*	24.9±1.0*	24.5±1.1*	
	50 MPC	***L***	63.4±2.7	53.2±5.1	31.0±1.3	33.4±5.4			
		H	66.0±3.7*	68.5±5.3	41.0±5.8	32.0±3.6*			
Deviation from the control group (%)	5 MPC	***L***			-46.1	-30.7	-59	-81.4	
		H			-52.5	-72	-72	-84.1	
	10 MPC	***L***			-49.2	-60	-55.2	-71.3	
		H			-52.5	-83.6	-64.9	-65.5	
	50 MPC	***L***	-4.5	-27.9	-48.5	-44.5			
		H	-7.1	-3.7	-42.3	-55			
Exposure to UOD + Extract of licorice root	5 MPC	***L***							31.4±0.9***
		H							53.8±3.8*
	10 MPC	***L***							26.2±1.8
		H							42.5±3.7
	50 MPC	***L***	66.4±2.4	65.6±0.4	49.6±0.6	42.1±4.5			
		H	31.4±2.6*	75.3±6.4	66.9±6.6	69.5±5.8*			
Deviation from the control group (%)	5 MPC	***L***							-47.7
		H							-24.4
	10 MPC	***L***							-56.4
		H							-40.2
	50 MPC	***L***	-	+7.4	-25.3	-30			
		H	-55.8	+5.8	-5.9	-2.3			
Deviation from the norm (%)	50 MPC	***L***	-	+23.3	+60	+26			
		H	-	-	+63.2	+117			

*- significant deviation from the norm, $p<0.05$
** - significant deviation from the control, $p<0.05$
*** - significant deviation from the control 5 MPC, $p<0.05$

Dynamics of the SOD activity in lung tissues was similar as a whole in rats exposed to the UOD in doses of 5 and 10 MPC (fig. 1). Nevertheless, the fluctuations of the SOD's activity in the lung tissues were observed. The inhibition of the activity of the antioxidative protection system occurs almost immediately with the smallest doses of the UOD. Thus the dynamics of the SOD's activity in lungs and in blood has shown essential dose and time dependence, and precise parallel with compensative and adaptive morphological and ultrastructural changes in lung tissue, details of which have been published previously (Jusmasheva RT, et al, 2006; Jumasheva RT, et al, 2009). So, if in the group of rats exposed to the UOD of 5 MPC, during their adaptation for 30 days to UOD exposure the SOD's activity

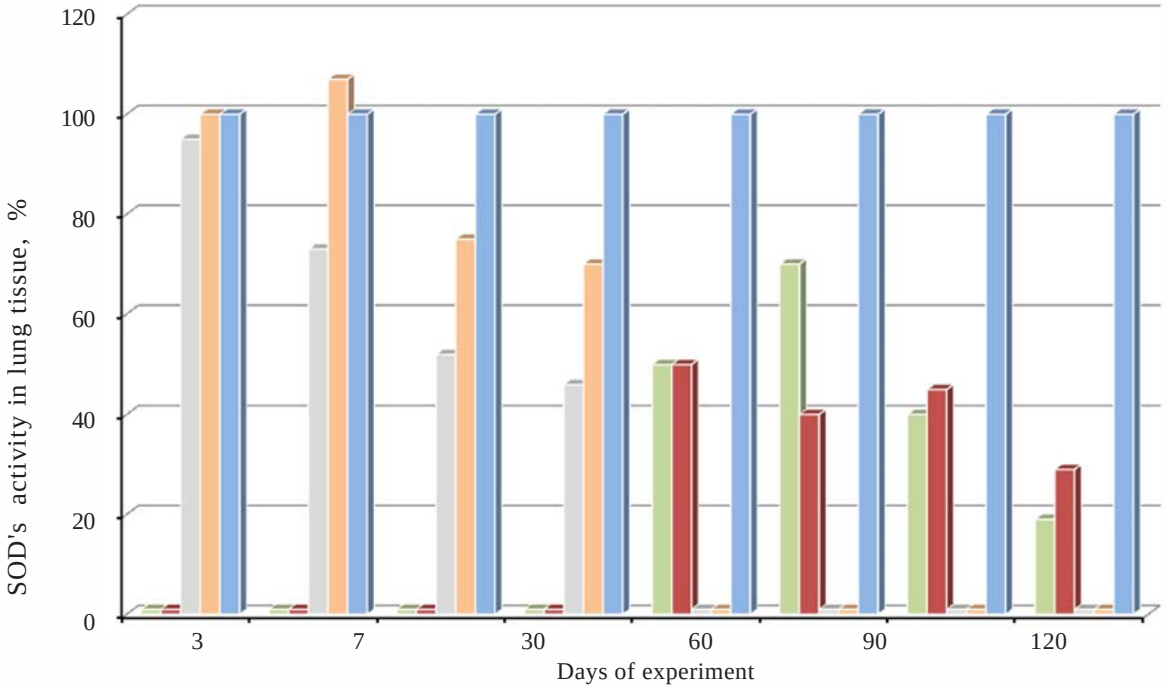

Fig.1 Dynamics of SOD's activity in lung tissue of rats exposed to different dose of uranium containing dust and treated by Licorice root extract.

Note: Обозначение доз - 5MPC; 10 MPC, 50 MPC; 50MPC+LRE, Control

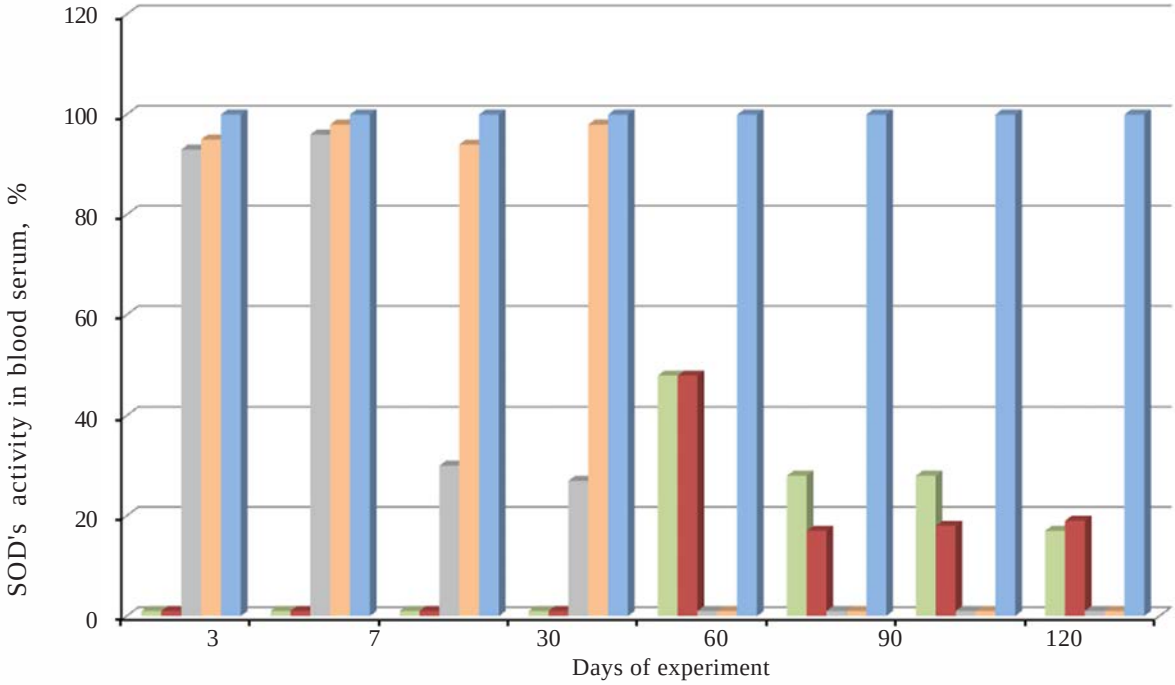

Figure 2 Dynamics of SOD's activity in blood serum of rats exposed to different dose of uranium containing dust and treated by Licorice root extract

Note: Обозначение доз - 5MPC; 10 MPC, 50 MPC; 50MPC+LRE, Control

changed within the limits of 33.7±0.95%, in the restoration period, it increased by 23.7 %. The transition into the phase of destructive reactions resulted in suppression of the enzyme's activity by 35 % with even more significant decreases in activity by day 120, the period of active destruction of the lung alveolus's epithelial lining.

The dynamics of the SOD's activity in the blood

serum during exposure by the UOD in different doses was found to be similar to activity changes found in the lung (Fig. 2). It is necessary to note that the lowest values of SOD activity were found during the highest content of malonedialdehyde, a lipid peroxidation biomarker, both in lung tissue and in blood serum.

In rats exposed to the UOD in the dose of 10 MPC, a stable 3 fold inhibition of SOD activity in the blood was established. These changes emphasize the long term nature of destructive reactions of lung tissues is reflected by dynamics of the activity of the enzyme in catalyzing redox reactions of superoxide radicals.

In rats exposed to the UOD in the dose of 50 MPC, the changes of the activity of the antiradical protection enzyme in lungs depend on duration of exposure of radiotoxic factors. The pattern of inhibition of SOD activity by the end of the 1st and even more significantly of the 2nd month could be the result of a depression of the enzyme's synthesis processes. It could as be explained by a loss of highly specific proteins in cells causing a decrease in cell membrane integrity and amplification of their fluidity. Therefore, the maximum inhibition of SOD in the blood, at almost 6 fold, was found earlier than corresponds to the time of transition of adaptive reactions into the destruction phase (Jumasheva RT, 2010).

We established that in the lung tissue of animals exposed to the long inhalation of the uranium ore dust in increasing doses, the activity of superoxide dismutase was reduced. This reduction continued to increase and occurred in complete conformity to the amplification of destruction in ultrastructural formations in the lungs.

Licorice root extract was found to mitigate the disorders of oxidative metabolism caused by UOD exposure. However, its efficiency depends on the significance of the damage and duration of radiotoxic action of the uranium dust. In rats exposed uranium dust by inhalation in doses of 5 MPC and receiving oral administration of LRE the SOD activity was increased 3x in the lung tissue and 5x in the blood serum by the end of the 5th month, in comparison with rats without LRE treatment. LRE treatment was found to be most effective in rats exposed UOD in doses of 50 MPC, with an increase in SOD activity by 60%, in lung tissue after 1 month and 117 % in blood serum, at the end of 2nd month. After two months, SOD activity in lung tissues did not exceed 26%. It is possible that an increased the dose LRE or a change in administration route could increase the efficacy of the LRE and result in a more dramatic change in SOD activity.

CONCLUSION

Exposure to the uranium dust in increasing doses inhibits the activity of the antioxidative protection of lung tissues and blood in a dose-and-time dependent manner. Oral administration licorice root extract of 100 mg/kg increased the activity of the superoxide dismutase in rats challenged with uranium dust in various doses.

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