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BIOLOGICAL SIGNIFICANCE AND TOXICOLOGICAL PROPERTIES OF IRON, SELENIUM AND IODINE

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ABSTRACT

Trace elements are the metals of life, their deficiency and excess in the body lead to metabolic disorders, which cause inhibition of growth and development of the body, a decrease in the intensity of digestive processes, and a disorder of the reproductive system function. Of particular importance are the trace elements selenium, iron, and iodine. Deficiency of a complex of trace elements (selenium, iron, zinc, and iodine) negatively affects all types of metabolism (protein, carbohydrate, lipid, etc.), and has adverse effects on health. This scientific work reveals in detail the biological role of iodine, selenium, and iron describes their significance for the human body, and also lists the main consequences of a shortage or overabundance of these trace elements in the body. In addition, the characteristics of the new drug SIF-Complex - a complex of iodine, iron, and selenium are given, and its main physico-chemical parameters are described. The new drug is being tested for acute toxicity, chemical toxicity, and irritant effect on white mice, white rats, and rabbits. The dynamics of the body weight of animals and their condition are monitored. Studies of rat blood and the condition of their internal organs were carried out. Conclusions are made about the low toxicity of the drug.

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Introduction

The functions of mineral substances in the human body are extremely diverse and determine its condition. The main ones are as follows: participation in the construction of tissues, maintenance of homeostasis of the internal environment of the body, ensuring the balance of cell membranes, activation of biochemical reactions through enzymatic systems, direct or indirect influence on the function of endocrine glands, impact on the symbiotic microflora of the gastrointestinal tract and others [1].

The main way of the effect of trace elements on the body is expressed by their inclusion in the composition of proteins, nucleic and amino acids, and biocatalysts, as well as participation in the maintenance of ion transport [2]. Trace elements after absorption in the intestine are transported by blood, deposited mainly in the liver, and are included in the composition of various enzymes, hormones, vitamins, and other biologically active substances [3-5]. In the body, bioelements can pass into complexes from organic matter bound to inorganic compounds, to the ionized state and back [6, 7].

Their functions are diverse: activation or inhibition of the action of many vitamins, hormones, and enzymes and this ensures their physiological activity and intensity of metabolism. Minerals and water in the body are in a state of constant exchange. Mineral substances in the form of inorganic salts with water cause the body to maintain the necessary osmotic pressure of blood, lymph, and other fluids. Through them, the constancy of the concentration of hydrogen ions and acid-base balance is maintained, and the excitability of the nervous system changes. Bioelements in the body are contained in various states: for

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example, in bones in the form of mineral gels, in soft tissues -true or colloidal solutions and compounds with proteins, being an integral part of proteins, carbohydrates, and fats that constantly interact with minerals [8, 9].
Trace elements are the metals of life, their deficiency and excess in the body lead to metabolic disorders, which cause inhibition of growth and development of the body, a decrease in the intensity of digestive processes, and a disorder of the reproductive system function. Of particular importance are the trace elements selenium, iron, and iodine. They influence biological processes in small doses while interacting with various biologically active substances [10, 11].
Deficiency of a complex of trace elements (selenium, iron, zinc, and iodine) negatively affects all types of metabolism (protein, carbohydrate, lipid, etc.), and has adverse effects on health. With a deficiency of trace elements, the body receives less complete protein, volatile fatty acids, B vitamins, and trace elements themselves [12].
Studies conducted over the past decades have shown that selenium is extremely necessary for the growth, development, and existence of animals and humans. Vitamin E and selenium have been shown to prevent peroxidation of the microsomal and mitochondrial membranes of liver cells, protecting fatty acids from oxidation, destroying peroxides, and suppressing the formation of free radicals [13, 14]. Selenium in the oxidation processes performs one function – neutralize toxic products of free radical reactions, and the therapeutic effect of selenium is necessary for optimal protection of cells and tissues from the effects of free radicals [15]. DNA-tropic action was revealed for selenium. Thus, when various selenium compounds are introduced into the reaction medium, RNA synthesis is inhibited. Probably, with a decrease in the concentration of selenium in the blood, the transcription process and the associated process of a malignant growth are activated [16, 17]. Selenium promotes the rejuvenation of cellular and organoid membranes, normalizes the activity of nuclei, and activates glutathione peroxidase, which is highly active in the liver, erythrocytes, kidneys, myocardium, skeletal muscles, and the reaction rate catalyzed by glutathione peroxidase is directly proportional to the content of the element in the diet [18, 19].
Iron has one of the most important values in human life, it is responsible for the production of hemoglobin in the blood, which supports the nutrition of organs, tissues, and systems. Without iron, red blood cells will not be able to function properly, which will lead to oxygen starvation. These processes negatively affect the body, most of all the heart and brain suffers from a lack of oxygen [20]. The adult human body contains about 3.5 grams of iron (about 0.02%), of which 78% is the main active element of blood hemoglobin, and the rest is part of the enzymes of other cells, catalyzing the processes of respiration in them. Iron is vital for the normal functioning of the immune system (T-lymphocytes, phagocytosis). It is necessary for the formation of bones and the nervous system, and for the work of the gastrointestinal tract, and endocrine glands [21]. Insufficient preventive and therapeutic effectiveness of existing iron-containing drugs, as well as the presence of side effects, is a prerequisite for the relevance of the development of new ferropreparations devoid of these disadvantages [22].
Iodine is the only trace element currently known to be involved in hormone biosynthesis. The mechanism of thyroxine formation is associated with the capture of inorganic iodides by the thyroid gland from the blood, and their oxidation to molecular iodine, which binds to tyrosine, forming mono- and diiodothyrosine. Two molecules of iodothyrosine form thyroxine– a thyroid hormone. Iodothyrosine, absorbed into the intestine, enters the liver, where, under the action of deiodinase enzymes, iodine is cleaved off as much as the body needs in accordance with the activity of this enzyme in the liver. The remaining amount of iodized amino acids in the form of glucuronides is excreted from the body through the intestines. Thus, there is a regulation of iodine metabolism in the body, eliminating overdose and excessive accumulation of it [23]. Iodine plays a significant role in the metabolism of carbohydrates and fats. When various animal compounds are introduced into the body, the sugar content in the blood increases, which is due to an increase in glycolytic activity and an increase in the breakdown of glycogen in the liver. At the same time, the content of neutral fat and cholesterol decreases [24]. Iodine increases the absorption of carbohydrates and their utilization increases the rate of glycolytic processes in the muscles, and liver, reducing the concentration of pyruvic acid in the blood. Active iodine exhibits antimicrobial properties by penetrating through the cell membrane of microorganisms and coagulating the cell protein. In this case, the primary connection between the cell and the drug is the electrostatic interaction. Therefore, its wide antimicrobial spectrum and the absence of resistance of microorganisms to it are understandable. The last two circumstances make it possible to start treatment without first determining the sensitivity of pathogenic microflora, which is especially important when eliminating the consequences of mass lesions [25]. The antimicrobial effect is enhanced by the repeated application of weak iodine solutions to the skin [23]. It enhances the processes of the assimilatory phase of protein metabolism and promotes the assimilation of phosphorus, calcium, and iron by the animal body. In elevated doses, iodine accelerates nitrogen metabolism. An excess of calcium and phosphorus in the animal's body leads to a decrease in the iodine content in the blood. In terms of the breadth of the antimicrobial spectrum, iodine-high copolymers far surpass all known antibiotics and sulfonamides. They are devoid of side effects and all the disadvantages inherent in all sulfonamides and antibiotics [25].
The main object of the study is the preparation of SIF-Complex, a complementary preparation of selenium, iron, and iodine.

Materials and Methods

During the experiment, we carried out toxicological, morphological, and biochemical research methods.
The toxicological properties of the drug were studied by determining acute and subchronic toxicity, the general effect on animals, their organs, and body systems, as well as local irritant, teratogenic, embryotoxic, and allergizing effects, effects on blood parameters, with pathomorphological studies of animal organs and tissues after the application of SIF-Complex, effects on the functions of digestive organs and urination.

The acute toxicity of SIF-Complex was determined in white rats by a single intragastric administration of the drug.

Indicators for determining acute toxicity were: animal appearance, condition, gait change, reactions to external stimuli, discharge from the eyes, and mouth, muscle twitching, tremor, convulsions, paralysis, paresis, etc.

During clinical observations, appearance, behavior, feed intake, body weight changes, and morphological and biochemical picture of blood were taken into account.

The subchronic toxicity of SIF-Complex was studied in white rats. The drug was given in a mixture with feed at the recommended therapeutic dose and a dose three times higher than the therapeutic dose for 21 days. Control animals were given a saline solution in similar volumes. The nature of the toxic effect was recorded by the number of dead animals and the picture of intoxication.

During daily observations, the general condition and behavior of animals (appetite, arousal, or depression), changes in reactions to external stimuli, the functions of the digestive and urination organs, and the dynamics of body weight gain were taken into account. Clinical symptoms of poisoning and the number of sick and fallen animals were noted.

For hematological studies, blood was obtained from rats from the heart. The blood was examined by conventional methods, while its main morpho–biochemical parameters were determined: the content of erythrocytes, leukocytes, hemoglobin, leukoformula cells.

The content of erythrocytes and leukocytes was determined by counting them in a counting chamber with a Goryaev grid; hemoglobin – hemoglobin-cyanide method (with acetone anhydrin); erythrocyte sedimentation rate – Panchenkov micrometer; hematocrit number – by centrifugation of blood in a capillary tube with subsequent determination of the result on a reference scale; blood enzyme elements – by a unified method of morphological examination with differentiated counting leukocyte formula; color indicator – calculated by the formula.

The local irritant effect of SIF-Complex was tested on rabbits by skin applications and conjunctival tests.

Results and Discussion

Characteristics of the Complex Preparation of Iodine, Selenium, and Iron

SIF-Complex is a complex preparation that contains the following active ingredients: 16-20 mg/ml of iron, 5.5–7.5 mg/ml of iodine, 0.07-0.09 mg/ml of stabilized selenium (corresponds to 0.16-0.20 mg/ml of sodium selenite).

SIF-Complex is a sterile, non-volatile opaque liquid of dark brown color, that mixes well in all ratios with water. There may be a small amount of sediment. The freezing point of the drug is about -30℃, the boiling point is about 103℃, the viscosity does not exceed 20 Stokes units, and the density is 1.03 – 1.05 g / cm^3. SIF-Complex is stored with caution in a dark place at a temperature from -2 to +30 ℃. The physico–chemical parameters of SIF-Complex should correspond to the data presented in **Table 1**.

Table 1. Physical and chemical parameters of SIF-Complex

№	Name of the indicator	Characteristic
1	Appearance	Opaque dark brown liquid
2	Iron (III) content, mg/ml	18 -20
3	Iodine content, mg/ml	5.5 - 7
4	The content of stabilized selenium, mg/ml	0.07 – 0.09
5	PH	7.0
6	Relative viscosity, no more	8
7	Sterility	Sterile
8	Toxicity	Non-toxic

In appearance, SIF-Complex is a dark brown (brown) colored liquid without the presence of sediment. The toxicity test was carried out on healthy white mice of both sexes weighing from 19 to 21 g. Each batch of the drug was tested on 5 mice. The test dose is 0.2 ml of the drug intravenously. The withdrawal rate is 30 seconds. The animals were monitored for 48 hours. The drug was considered to have passed the test if none of the experimental mice died during the prescribed observation period.

Acute Toxicity of the Drug

Acute toxicity was studied on white mice of both sexes weighing 20-22 g. The drug was administered once intramuscularly to five groups of 6 animals in each group in different doses: 0.5, 0.6, 0.7, 0.8, 0.9 ml per head. Animals of the control group were injected intramuscularly with saline in a dose of 0.9 ml.

15-20 minutes after administration of the drug, the animals appeared restless, agitated, and increased water consumption was observed. Excitement was gradually replaced by depression and loss of appetite, shortness of breath, tetanic spasms, and death from respiratory failure. In the surviving animals, these signs gradually passed, and after 48 hours the animals did not differ clinically from the control ones. When pressing on the injection site, soreness persisted for 3-4 days.

No acute inflammatory reaction and necrosis foci were found at the injection site upon autopsy. Intense brown coloration of the injection site and adjacent tissues was noted.

According to the results of calculations (SPSS for Windows) for white mice, the LD50 of SIF-Complex preparation with intramuscular administration is 32.14 (28.43 – 35.67) ml/kg of weight.

In the second series, acute toxicity was studied on white rats of both sexes weighing 220 – 240 g. The drug was administered once intramuscularly to five groups of 6 animals in each group at a dose of 6,7,8,9 and 10 ml per head. Animals of the control group were injected intramuscularly with saline in a dose of 10 ml.

Clinical signs similar to white mice were observed in rats after administration of the drug. 15-20 minutes after administration of the drug, anxiety was observed in the animals of the experimental groups. The first animals died an hour after injection with signs of respiratory failure. The death of animals was observed during the day. After 48 hours, the surviving animals did not differ clinically from the control animals.

No acute inflammatory reaction and necrosis foci were found at the injection site upon autopsy. According to the results of calculations for rats, the LD50 of SIF-Complex preparation with intramuscular administration is 34.54 (31.41 – 37.56) ml/kg of weight.

Determination of Chronic Toxicity

The purpose of studying this toxicity is to identify the selective effect of SIF-Complex on the functional state of individual organs, tissues, and systems, as well as its ability to accumulate.

The study of subacute toxicity was carried out on 30 rats selected according to the principle of analogs for 28 days. The drug was given with feed daily in doses of 1/3 of LD50. The animals were monitored daily, appetite, motor, and behavioral reactions were taken into account, individual weighing was carried out, and biochemical and morphological blood tests were carried out before the next increase in the dose of the drug. The dead animals were opened. The dose of the drug individually for each animal was dissolved in a small amount of hot vegetable oil and thoroughly mixed with the feed.

The death of animals was observed 15-20 days from the beginning of the experiment.

Upon autopsy of individual animals, no visible changes in the heart, brain, or gastrointestinal tract were detected. Brown staining of the injection site and adjacent tissues was noticeable. Marked hyperemia of the liver. There was noticeable hyperemia in the kidneys and a more pronounced border between the cortical and cerebral layers. There were no signs of tissue irritation at the injection site. Studies have shown that the drug has low accumulation and low chronic toxicity.

The chronic toxicity of SIF-Complex was studied in another series of experiments on white rats. At the same time, the drug was administered orally in optimal and three-fold therapeutic doses at a time three times higher than recommended.

The animals were selected and distributed into groups according to the principle of paired analogues, kept in identical feeding and maintenance conditions. The number of animals in the groups was determined by the expediency of an objective assessment of the results obtained and their statistical reliability.

A series of experiments were carried out in vivarium conditions on 30 mongrel white rats divided into three equal groups weighing 190-200 grams. In the first group, the drug was given to animals together with a combined feed at a dose of 1.2 ml/kg (a three-fold therapeutic dose), and in the second - 0.4 ml/kg (a single therapeutic dose), daily for 21 days (three times the recommended duration of administration of the drug). The third group of animals was a control, which was kept on the main diet, and did not receive the drug.

Clinical observations were conducted for all animals during the entire period of administration and seven days after discontinuation of the drug, paying attention to the general condition, behavioral reactions, appetite, dynamics of animal weight gain, the time of occurrence and nature of intoxication, its severity, and reversibility. The experimental animals were weighed at the beginning and end of the experiments. For biochemical and morphological studies, blood was taken from the heart using a monovet. Internal organs (heart, lungs, kidneys, spleen, liver, stomach, large and small intestines) were weighed in 5 rats of each group. Selected material for histological studies.

As a result of the experiments conducted, it was found that repeated use of SIF-Complex in optimal and triple therapeutic doses does not have a toxic effect on the body of white rats. Throughout the entire duration of the experiment, they remained mobile with a well-expressed appetite, their behavioral reactions remained normal, and their reflexes were preserved and did not differ significantly from those of control animals. The conducted weighing showed that the administration of the drug in single therapeutic doses contributed to an increase in the body weight of animals **(Table 2)**.

Table 2. Weight change in white rats with the internal administration of SIF-Complex

Group	Average weight of one rat, grams		Average daily weight gain	
	The beginning of the experience	The end of the experience	mg	In % to control
1	198.4	205.1	307	111.2
2	198.2	204.4	296	103.8
3	199.0	204.9	285	-

In this series of experiments, the average daily gain of one rat averaged 296 mg in the second experimental group and 285 mg in the control group. The administration of triple therapeutic doses of SIF-Complex also did not significantly affect the weight gain of experimental animals and did not have a pronounced toxic effect on their body **(Table 3)**.

The conducted weighing of internal organs (heart, liver, kidneys, small and large intestines) showed that the average weight of all these organs of experimental white rats did not differ significantly from those of the control group animals. Only in animals of the first group, there was a slight increase in the mass of the liver, stomach, and intestines.

Table 3. Effect of SIF-Complex on the mass of internal organs of rats (M±m)

Group	Weight of organs, grams						
	liver	**spleen**	**heart**	**lungs**	**kidneys**	**intestine**	**stomach**
1	11.84±0.1	1.22±0.03	1.32±0.04	2.28±0.17	2.30±0.13	29.12±0.53	11.31±0.51
2	11.56±0.09	1.18±0.04	1.30±0.03	2.26±0.12	2.32±0.10	28.96±0.63	11.01±0.71
3	11.54±0.13	1.24±0.02	1.32±0.04	2.32±0.12	2.44±0.3	28.88±1.01	10.91±0.81

The blood test confirmed the conclusion about the low toxicity of the drug. At the same time, all analyzed blood parameters of experimental animals did not differ significantly from those in the control **(Table 4)**.

Table 4. Effect of SIF-Complex on rat blood counts (M+m)

Indicators	Groups		
	Control	**Experience 1**	**Experience 2**
Red blood cells, 1012/l	5.94±0.07	8.2±0.09	8.7±1.04
Leukocytes, 109/l	9.58±0.34	9.54±0.21	8.91±1.07
Hemoglobin, g/l	138.0±12.6	142.0±11.3	139.5±14.35
Eosinophils, %	2.2±0.37	3.4±0.24	2.8±0.34
Neutrophils, %	30.6±2.81	35.2±411	33.11±3.64
Basophils, %	1.0	0	0
Lymphocytes, %	66.2±3.40	64.8±4.20	63.02±6.93
Monocytes, %	2.44±0.51	2.2±0.37	1.07±0.13
Total protein, g/l	70.5	68.59±5.9	68.01±7.48
Albumins, %	36.2±1.86	37.1±1.01	36.91±4.06
Globulins, %	63.8±2.16	62.9±4.16	63.09±7.7
Protein coefficient.	0.56	0.59	0.58
AsAT, units/l	123.7±16.4	134.8±22.6	132.7±14.59
AlAT, unit/l	72.6±8.1	69.3±11.3	68.1±8.17
Total bilirubin, mmol/l	4.12±0.51	3.96±0.44	3.28±0.36
Urea, mmol/l	7.41±0.81	6.91±0.76	6.95±0.83
Creatinine, mmol/l	27.8±3.06	31.4±3.77	30.61±3.67
Cholesterol, mmol/l	1.76±0.19	1.8±0.21	1.72±0.19
Calcium, mmol/l	3.83±0.42	3.34±0.4	3.51±0.42
Phosphorus, mmol/l	3.63±0.39	3.56±0.39	3.42±0.41
Magnesium, mmol/l	1.71±0.20	1.81±0.23	1.53±0.20

The Study of Irritating Action

To experiment to study the irritating effect of the drug, 5 rabbits aged 7.5 months were used. The animals were about the same weight (2.56+0.15 kg). The tests were carried out by the method of conjunctival samples. The drug was administered at the rate of 1 mg for injection per 1 ml of water. The drug was injected into rabbits under the upper eyelid, using an eye pipette, one drop was into the right eye, and a drop of distilled water was injected into the left eye as a control.

The animals were observed for an hour. In the first minute after administration of the drug, the animals showed slight excitement, as well as increased activity, but there was no itching and attempts to comb the eyes with paws.

30 minutes after administration of the drug, rabbits had a slight change in the right eye - the conjunctiva acquired a faint pink hue, and there were no visible changes in the left eye.

Examination of rabbits was also carried out 12 hours and a day after administration. There were no visible differences between eye conditions. This indicates that the drug SIF-Complex does not have a pronounced irritant effect and it can be freely used for injection.

Conclusion

SIF-Complex is a preparation containing selenium, iron, and iodine. The content of stabilized selenium is 0.07-0.09 mg/ml, iron (III) – 18-20 mg/mg body weight, and iodine – 5.5-7 mg/ml. SFJ-Complex is low toxic for white mice and white rats. According to the results of the calculations for white mice, LD50 with intramuscular administration is 32.14, white rats – 34.54 ml/kg of body weight.

The manifestation of the toxic effect of the drug began 20 to 30 minutes after administration and stopped within a few hours, the death of animals occurred after 12 to 48 hours. They experienced agitation, which was replaced by depression and loss of appetite, shortness of breath, tetanic enemas, and death from respiratory failure.

At the autopsy, stagnant phenomena were observed in the liver and other parenchymal organs.

When administered orally, the drug in an optimal and three-fold therapeutic dose to white rats does not have a toxic effect on the body of white rats. The body weight was slightly higher in the experiment 296 g versus 285 in the control. The mass of internal organs did not differ significantly, and blood counts were not noted.

The drug stimulates erythro- and hematopoiesis and increases the content of iron, iodine, and selenium in the blood.

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Conflict of interest: None

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Ethics statement: The protocol for experiments with laboratory animals complied with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes. Also, the experimental work with animals did not contradict the internal regulations of the ethical councils of the Astrakhan State Medical University, Dagestan State Medical University and Rostov State Medical University.

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