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ASSESSMENT OF THE PHARMACOLOGICAL EFFICACY OF A NEW ANTI-DIABETIC DRUG

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ABSTRACT

Diabetes mellitus is today one of the global medical and social problems in the health care system. According to the International Diabetes Federation (IDF), there were more than 425 million type II diabetes patients worldwide in 2019. **Purpose of the study.** To study preclinical pharmacological and toxicological studies of a new drug obtained on the basis and evaluate its hypoglycemic effect. **Materials and research methods.** The study of the acute toxicity of the new antidiabetic drug was carried out on 20 sexually mature white male rats with an initial body weight of 160-183 grams, exposed to intragastric doses of 500, 550, 600 and 650 mg / kg. The animals were injected intragastrically at 3.0 ml / 100 g. body weight. **Research results.** Observation of experimental animals with acute toxicity of the herbal preparation for 14 days, there were no pronounced symptoms of intoxication in animals. In groups of 6 animals receiving 550 mg / kg, 1 died, 1 received 600 mg / kg-2, and 650 mg / kg-4. Experienced animals responded adequately to external stimuli. Visible mucous membranes are moist, pale pink in color, shiny and smooth in appearance, no foci of baldness were found.

Key words: Phytodiabetol, mucous membrane, phytopreparation, acute hyperglycemia, Marey capsule.

INTRODUCTION

Relevance. Diabetes mellitus is today one of the global medical and social problems in the health care system. According to the International Diabetes Federation (IDF), there were more than 425 million type II diabetes patients worldwide in 2019 [1,4].

The medical and social significance of diabetes is attributed to the serious complications of the disease, the high prevalence of disability and the number of deaths. To prevent and treat this pathology, it is important to study the pharmacotoxicological properties of drugs obtained from plants [6,8].

In the world, pharmacotoxicological studies of drugs used to treat diabetes mellitus and its complications, which have different effects on metabolic processes, are being carried out [10, 12]. Particular attention is paid to the development of biologically active drugs based on local medicinal plants and providing the population with inexpensive local drugs.Despite the evidence that many plants have antidiabetic properties to one degree or another, a number of studies, as well as traditional practice, confirm that one of the the most effective of these are blueberries and Galega officinalis. The studied phytopreparation contains blueberries and Galega medicinalis (Galegaofficinalis) [15,16,19,20].

In this regard, it is necessary to assess the pharmaco-toxicological efficacy of the herbal preparation obtained on the basis of medicinal plant extracts Vaccinium myrtillus L. and galega officinalis L.

Thus, for the first time preclinical studies of a new antidiabetic phytopreparation were carried out, and in the future, its introduction into clinical practice will be a highly demanded and urgent task.

Purpose of the study. To study preclinical pharmacological and toxicological studies of a new drug obtained on the basis and evaluate its hypoglycemic effect.

Materials and research methods. The study of the acute toxicity of the new antidiabetic drug was carried out on 20 sexually mature white male rats with an initial body weight of 160-183 grams, exposed to intragastric doses of 500, 550, 600 and 650 mg / kg. The animals were injected intragastrically at 3.0 ml / 100 g. body weight. The chronic toxicity of the phytopreparation was studied under conditions of intragastric exposure on white rats at doses of 6, 60 and 120 mg / kg for 30 days. The experiment used 24 white male rats with an initial body weight of 162-180 g. We study the effects of the new drug on blood pressure and respiration under conditions of acute experience on 4 cats and 2 rabbits weighing 2.5-3.5 kg of both sexes [2,3]. The experiment was carried out under urethane anesthesia. Urethane was injected intraperitoneally at a dose of 1-1.2 g / kg. Blood pressure was recorded on an electrokymograph tape from the common carotid artery

through a system of polyethylene tubes with a Ludwig mercury manometer. The system was filled with 5% sodium citrate solution, and 0.015 ml of heparin solution was added to the solution in the area of the arterial cannula. In parallel, respiratory movements were recorded using a Marey capsule connected to the trachea of the animal [5,7,9].

In the next series of experiments, the effect of the herbal preparation on the bioelectric activity of the heart was studied. For the experiment used 2 rabbits, weighing 2.8-3.3 kg and 8 rats, weighing 154.3-167.8 g, of both sexes. The study drug was administered to animals orally at doses of 5, 10 ml / kg. Electrocardiograms of experimental animals were recorded before and after drug administration.

The study of the local irritating effect of the liquid extract of the new drug in the first series of experiments on the conjunctival test was carried out on rats, guinea pigs and rabbits. Each experimental group consisted of 3-5 animals. Liquid extract in various concentrations and in the form of the method of evaporation in a dealcoholized form in 1-3 was applied to the conjunctival sac of the right eye. The right eye of guinea pigs and rabbits. The left eye was the control one. The reaction of the conjunctiva to the substance in a concentration of 0.25-1.0% solution and the dealcoholized form in a dilution of 1/10 was assessed after 5 ', 15', 30 ', 60' minutes and after 6 and 24 hours. In the second series of experiments, the studied phytopreparation in concentrations of 10, 20, 40% solution was injected into the oral mucosa of rats, guinea pigs and rabbits in a volume of 2-5 drops, as well as by oral administration with a special metal probe in doses of 2.5, 5 ml / kg and 10 ml / kg. The results of the experiment on mice and rats studied the irritating effect of the phytopreparation on the skin. At the same time, for two weeks, pre-sheared wool was lubricated with a size of 1 cm × 1 cm and 2 cm × 2 cm, the studied concentrations and the de-alcoholized form. Experiments on the study of cumulative properties were carried out on 30 rats, weighing 138-155 g of both sexes, the animals were divided into three groups of 10 rats per group. The studied liquid extract of the phytopreparation was administered orally with a special metal probe with olive to the first group of animals, and the second group was injected with the dealcoholized form of the phytopreparation [11,13]. The third group was the control group. In the first 5 days, the studied phytopreparation was injected, respectively, 1 ml and 1.5 ml per animal weight.

The model of acute hyperglycemia was induced according to the method described in the book by O. V. Remizov and T. L. Kuraev. In order to exclude the influence of food on the absorption of the test substance, the feeding of the animals was stopped 4-6 hours before the experiment. Longer fasting is undesirable due to

the fact that in this case the severity of the hypoglycemic effect of the drug decreases [14,17,18]. Experimental hyperglycemia in rats was induced by a single intraperitoneal injection of a hypertonic glucose solution at a dose of 4.5 g / kg. 30 minutes before glucose administration, the test substances were administered orally in the form of a 10% aqueous solution using a probe. After 30, 60, 90 and 120 minutes, the blood glucose level was determined by the enzymatic method. Determination of glucose was carried out in blood serum by the enzymatic method. On the model of acute hyperglycemia, the activity of a new herbal preparation was compared with the well-known hypoglycemic drug - domestic Gluqueir (50 mg / kg). For this, Phytodiabetol was used in doses of 6 and 60 mg / kg. The experiments were carried out on 24 sexually mature white rats weighing 160-180 g.

Research results. Observation of experimental animals with acute toxicity of the herbal preparation for 14 days, there were no pronounced symptoms of intoxication in animals. In groups of 6 animals receiving 550 mg / kg, 1 died, 1 received 600 mg / kg-2, and 650 mg / kg-4. Experienced animals responded adequately to external stimuli. Visible mucous membranes are moist, pale pink in color, shiny and smooth in appearance, no foci of baldness were found.

It was found that the reaction of animals in the first 1-1.5 hours is somewhat inhibited, the rats are passive. The symptoms disappeared after 2 days of the experiment. LD50 was calculated using the Stat plus-2009 probit analysis software package.

The results of the experiments on the study of the acute toxicity of Phytodiabetol showed that with a single intragastric administration, the LD50 of the drug was 606.41 (512.29-698.53) mg / kg. Due to the fact that this dose is 120 times higher than the average daily therapeutic dose, the phytopreparation can be classified as low-toxic. And it was also revealed that the results obtained confirm the absence of a negative effect of the studied doses of the phytopreparation on the dynamics of changes in the body weight of laboratory animals. Macroscopic pathological and anatomical studies of internal organs showed that Phytodiabetol did not cause toxic degenerative changes in the most important internal organs.

The results of the studies have shown that long-term oral administration of Fitodiabetol at doses of 6, 60, 120 mg / kg is well tolerated by experimental animals. All experimental animals did not differ from control rats in general condition, behavior, weight gain and hematological parameters (Table 1).

Table 1

Changes in hematological parameters of rat peripheral blood under the influence of phytopreparation

Groups doses	Leukocytes, 10 9 / l	Absolute lymphocyte count, 10 9 / l	The absolute content of a mixture of monocytes, basophils and eosonophils, 10 9 / l	The number of granulocytes, 10 9 / l	Hemoglobin, g / l	Erythrocytes, g / l RBC	Hematocrit, % HCT	Average concentration of hemoglobin in erythrocyte, g / l	Platelets in absolute numbers, 10 9 / l	Thrombokrit, %
Control	15,88±0,47	7.56±0.42	2,8±0,24	5.2±0,35	136±3,71	6,52±0,22	36,48±1,08	371,2±5,36	588,2±41,82	0,454±0,04
6 mg / kg	14,36±0,56	6,04±0,40	2,32±0,22	5,2±0,39	129,4±3,86	6,80±0,18	35,62±1,06	360,8±4,99	558,6±40,66	0,508±0,05
60 mg / kg	13,78±0,31	6,18±0,53	2,42±0,33	5,14±0,41	125,6±3,94	6,64±0,20	34,88±1,22	362,6±5,02	601,8±50,76	0,521±0,04
120 mg / kg	14,66±0,42	6,4±0,36	2,76±0,29	5,08±0,36	127,8±3,55	6,72±0,26	35,42±1,26	363,2±5,08	560,2±51,86	0,507±0,04

Biochemical studies of blood serum were carried out 30 days after subchronic intragastric inoculation of animals. The study of the dynamics of the content of ALT, AST, alkaline phosphatase in the blood serum did not reveal statistically significant differences in the rats of the experimental groups in comparison with the control data. Data analysis of peripheral blood parameters and indicators of alkaline phosphatase, trans-aminase enzymes (ALT, AST) in the blood serum of animals indicates that the phytopreparation in the studied doses does not significantly affect the tested parameters. That is, the indicators of alkaline phosphatase, trans-aminase enzymes (ALT, AST) in the blood serum of the experimental animals did not differ significantly from the control values. Changes were observed on the side of blood glucose concentration in rats taking the test drug, especially in a high concentration (Table 2).

Table 2

Changes in the biochemical parameters of the blood of rats taking phytopreparations

Groups	Alanine aminotransferase activity, ALT	Activity of aspartate aminotransferase, AST	Alkaline Phosphatase Activity, ALP	Glucose
	U / L (at 37^0C)			mmol / L
Control (intact)	74,42±6,14	270,2±12,39	392,46±40,25	6,45±0,26
6 mg / kg	79,38±6,97	276,6±11,19	322,40±32,36	4,92±0,30*
60 mg / kg	85,94±6,49	281,1±12,67	326,56±38,95	5,79±0,36
120 mg / kg	57,02±6,04	269,6±10,22	363,08±40,91	3,88±0,27*

Note: * -confidence at P <0.05 compared to control.

As can be seen from Table 2, oral intake of a phytopreparation by animals for a month at a concentration of 120 mg / kg leads to a 40% decrease in the concentration of glucose in the blood, which confirms the specific activity of this herbal preparation, and the absence of obvious deviations from the norm of such biochemical parameters as activity alkaline phosphatase, alanine and aspatrate aminotransferases indicate the low toxicity of this drug.

The results of the influence of the investigated phytopreparation on the content of immunoglobulins of the classes IgE, IgG, IgM in the blood serum of rats are presented in table. 3. Studies have shown that the drug in doses of 6.0 mg / kg, 60.0 mg / kg, 120.0 mg / kg do not have a significant effect on the content of immunoglobulins of the IgE, IgG and IgM classes in the blood serum of rats.

Table 3

Results of the influence of "Fitodiabetol" on the content of immunoglobulins of the classes IgE, IgG, IgM in the blood serum of rats

BAD	Dose of the drug, mg / kg	Concentration IgE, IU / ml	Concentration IgG, mg / ml	Concentration IgM, mg / ml
"Phytodiabetol"	6,0	5,20±0,71	2,60±0,21	0,12±0,01
	60,0	5,50±0,82	2,80±0,26	0,12±0,01
	120,0	5,60±0,90	2,90±0,30	0,13±0,02
Control	-	8,0±0,1	4,1±0,6	0,14±0,02

In the pathological study, carried out 30 days after the intragastric exposure to the phytopreparation, at doses of 6, 60 and 120 mg / kg, it was found that the appearance, size and macroscopic structure of internal organs in rats of the experimental groups did not visually differ from the control ones. These results confirm that the studied substances do not have toxic properties. All animals had the correct constitution, a neat appearance, and a shiny coat. Visible mucous membranes are moist, pale pink in color, shiny and smooth in appearance. The external genital organs of the males had no visible deformations or deviations from control. Light-optical microscopic examination of the internal organs of all experimental groups of animals revealed an identical histomorphological picture of the tissues of the studied organs.

Liver. The histomorphological picture of the liver after 30 days of intragastric administration of Phytodiabetic, regardless of the dose of exposure, revealed the same type of picture. The liver capsule in experimental animals is not thickened, it contains longitudinally oriented bundles of collagen fibers. The liver parenchyma is formed by the classic hepatic lobules, consisting of the hepatic plates or trabeculae radially oriented to the central vein. Hepatocytes are polygonal, with a centrally located nucleus (Figure 1-2).

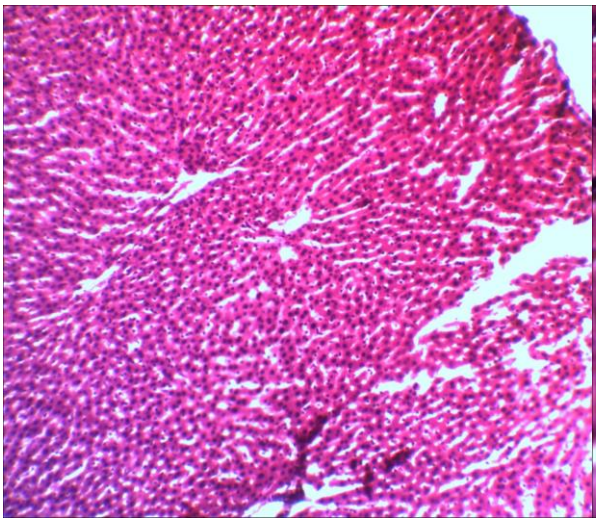

Fig. 1. Rat liver after intragastric exposure. The structures are not disturbed, there are no dystrophic changes. HE staining. About. 10x10.

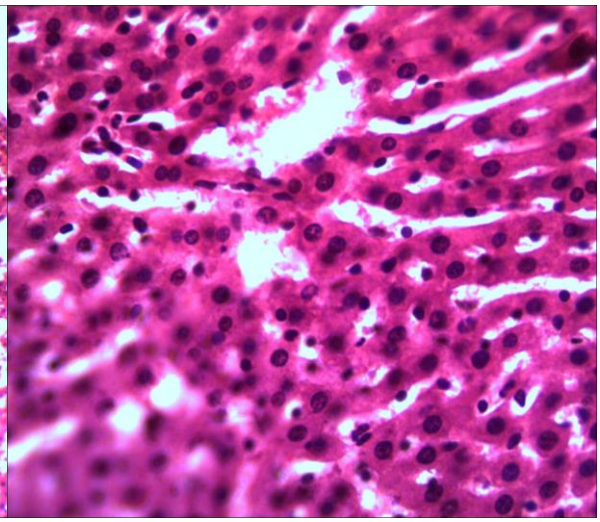

Fig. 2. Rat liver after intragastric exposure. Central Vienna. The structures are not disturbed, there are no dystrophic changes. HE staining. About. 10x40.

Stomach - in the esophageal and glandular parts of the stomach, regardless of the dose of exposure, dystrophic changes were not detected (Figure 3-4).

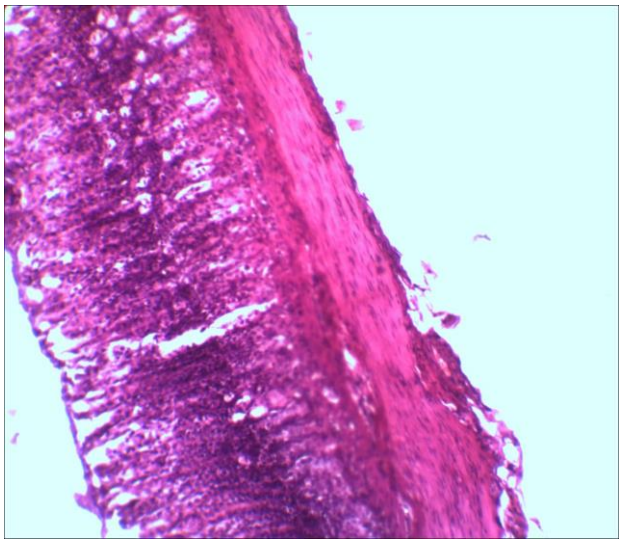

Fig. 3. The stomach is the glandular part. Mucous membrane, submucosa, glands. Cell structures are not disturbed, there are no dystrophic changes. HE staining. About. 10x10.

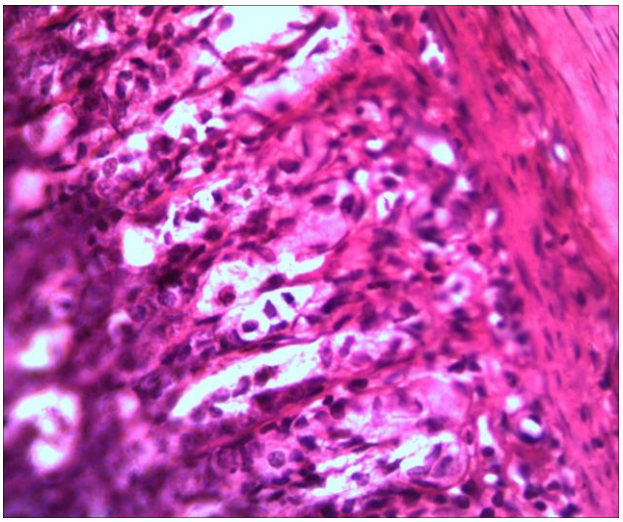

Fig. 4. The stomach is the glandular part. Major cells, parietal muscularis. The structures are not disturbed, there are no dystrophic changes. HE staining. About. 10x40.

Spleen - the study of lymphoid follicles, white and red pulp has established that the structure in the organ is not disturbed after prolonged intragastric exposure to the phytopreparation in the studied doses (Fig. 5-6).

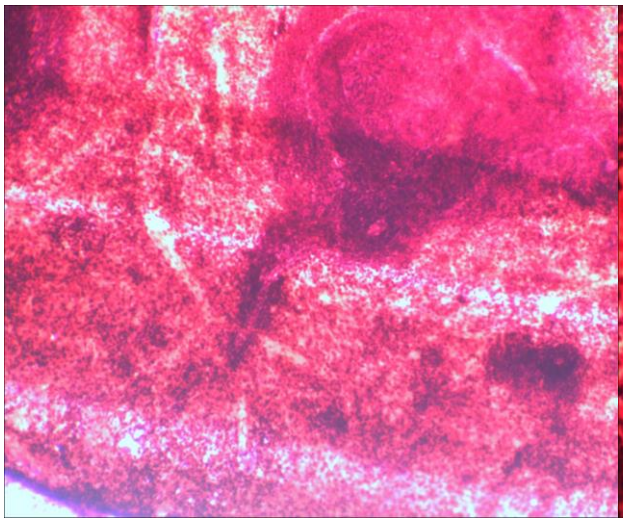

Fig. 5. Spleen. Lymphoid follicle, red pulp. The structures are not disturbed, there are no dystrophic changes. HE staining. About.10x10.

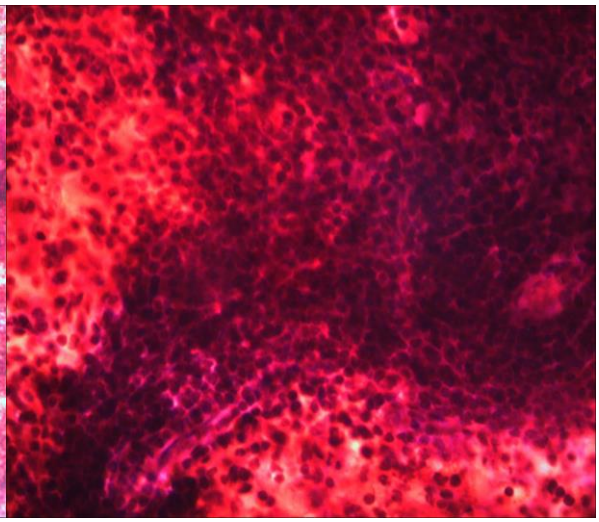

Fig. 6. Spleen Central artery of the follicle. The structures are not disturbed, there are no dystrophic changes. HE staining. About.10x40.

Kidneys. In the kidney tissue, no changes are also detected (Fig. 7-8).

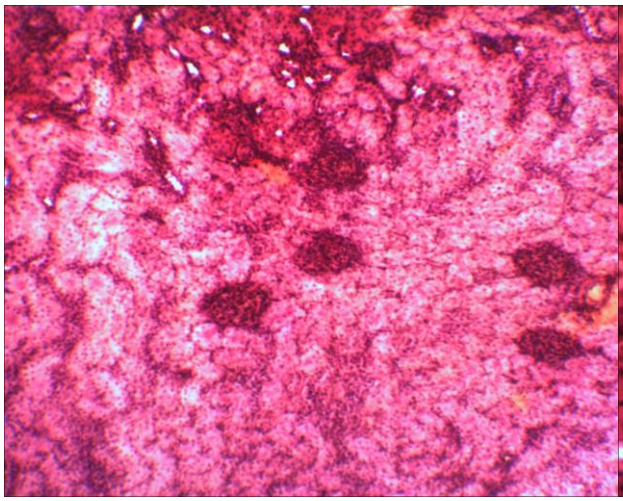

Fig. 7. Kidney cortex. Glomeruli, tubules. The structures are not disturbed, there are no dystrophic changes. HE staining. About. 10x10.

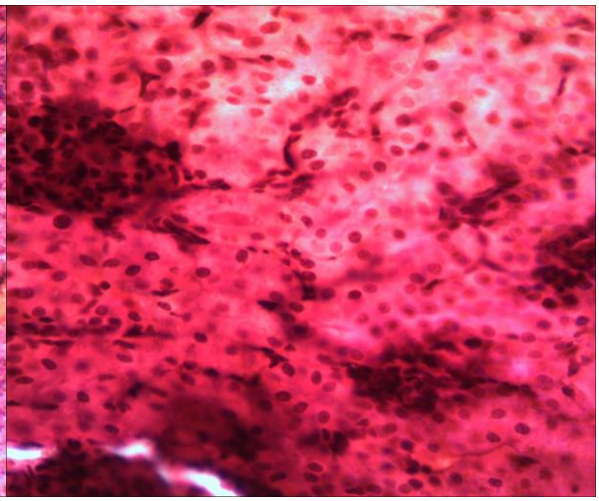

Fig. 8. Kidney cortex. The glomerulus, tubules. The structures are not disturbed, there are no dystrophic changes. HE staining. About. 10x40.

Based on the results obtained, it can be concluded that prolonged intragastric administration of the phytopreparation once a day does not lead to toxic damage to organs.

On the basis of a comparative histomorphological study of organs and tissues of control and experimental animals, it can be concluded that no necrosis, hemorrhages, dystrophic changes were observed in micropreparations of the stomach, liver, heart, lungs, kidneys of the spleen, regardless of the doses of the phytopreparation.

The data obtained on the study of the phytopreparation for blood pressure and the frequency of respiratory contractions showed that in doses of 5 and 10 ml / kg it slightly reduced blood pressure (by 5.2% and 6.4%) and briefly extinguished the frequency of respiratory contractions (by 2.7%). When a dose of 25 ml / kg is administered, it more pronouncedly reduces blood pressure (by 18.3%), which lasted no more than 23-35 minutes. The effect of the phytopreparation on blood pressure was more pronounced at a high initial pressure.

Analyzes of the bioelectrical activity of the heart showed that in all cases of animal experiments that received the drug in the studied doses, there were no significant changes in the heart rate, there were no intervals, and the amplitude of the ECG waves increased by 5.6%; 8.5% and 14.6% of the norm. The rhythm in all cases was sinus, the contractility of the myocardium of the atria (P wave) and ventricles (QRS) was normal and there were no changes in the conducting system.

Studies have shown that the studied liquid extract and its dealcoholized form do not have a local irritating effect, since no special changes were revealed during a visual macroscopic examination of the skin of animals in comparison with the control ones. 14-day observation of the state of the conjunctiva showed that the studied phytopreparation in the studied concentrations does not significantly irritate the conjunctiva of the eye. Also, the mucous membrane of the stomach and oral cavity of the experimental animals were normal and without signs of irritation and changes.

Therefore, we can say that the studied herbal preparation in the study of concentrations does not have a local irritating effect.

Experiments on the study of cumulative properties were carried out on 30 rats. In the next 5 days, respectively, 2 ml and 2.5 ml per animal weight, and on days 11-15 of the experiment, 2.5 ml and 4.0 ml per weight and in the next 5 days, respectively, 3 ml and 6 ml per masses of animals. The control group received distilled water according to the same scheme and dose of exchange. The condition of the animals was monitored visually, with the main attention being paid to the general condition, reactions to external stimuli, appetite and to the weight of the animals.

Experiments have shown that in both the experimental and control groups of animals there were no significant differences in weight. The mucous membrane and coat of all animals were unchanged. The animals enjoyed food and water. The respiratory rate in all groups of animals was the same, no gastrointestinal disturbances were observed. When the animals were dissected on the 20th day of the experiment, a normal histomorphological picture of the internal organs was

observed in all animals from the side of the vital internal organs, no visual changes were revealed.

The hypoglycemic activity of the drug has also been proven.

Table 3

Biochemical parameters of rat blood in an experimental model hyperglycemic type of diabetes formation (n = 6, M ± m)

Groups	Alanine aminotransferase activity, ALT	Alkaline Phosphatase Activity, ALP	Glucose, Glu	Total bilirubin, TBil	Direct bilirubin, DBil	Total protein, TP
	U / l (at 37^{0}C)		Mmol / l			g / dl (at 37^{0}C)
Control (intact)	79,03±3,75	890,67±45,68	4,77±0,71	16,63±1,36	8,15±0,70	104,72±7,42
Control (diabetes)	**76,47±4,24**	**1012,15±32,47**	**12,97±0,83**	**36,77±4,06**	**22,90±1,85**	**113,40±8,28**
Phytodiabetol 6 mg / kg	83,58±3,78	859,33±50,41*	3,92±0,76***	21,63±1,28**	10,55±0,48**	112,50±9,91
Phytodiabetol 60 mg / kg	77,20±4,16	852,35±40,90*	4,17±0,72***	19,02±1,95**	10,00±0,90**	110,43±9,26
Phytodiabetol 120 mg / kg	82,93±4,74	950,37±32,80*	2,06±0,76***	17,73±1,55**	9,62±0,86**	121,83±11,56
Glouqueir 6 mg / kg	78,08±3,16	915,72±42,70*	2,71±0,51***	19,60±1,45**	10,72±0,90**	121,57±10,38

Note: * P <0.05 compared to control;
** P <0.001 compared to control;
*** P <0.0001 compared to control

As can be seen from Tables 3, the concentration of glucose in the blood serum of diabetic control animals with high reliability (P <0.0001) exceeds the blood glucose concentration of animals in the intact control group, which indicates the effectiveness of the model of the hyperglycemic method of inducing diabetes in experimental animals. “Phytodiabetol”, like the reference drug “Glukeir” at concentrations of 6-120 mg / kg, with high reliability (P <0.0001) lower the glucose level to the level of the intact group and even lower. No changes in the enzyme alanine aminotransferase were observed in experimental animals. In this model, the activity of the enzyme alkaline phosphatase increased by one order of magnitude in animals without drug therapy, the activity of which decreased significantly (P <0.05) to the norm in intact animals in all animals taking the study drugs. In this model, the concentration of bilirubin, both direct and general, increased twofold in animals without drug therapy compared with intact animals, but these indicators decreased significantly (P <0.001) to the norm of intact animals in all animals taking Phytodiabetol drugs. and Glouqueir.

Conclusions.

1. According to the results of the experiments on the study of acute and chronic toxicity of the phytopreparation, it was experimentally proved that it belongs to low-toxicity drugs of the IV class.

2. With its subchronic administration, it was revealed that within 30 days the dynamics of hematological parameters, the content of ALT, AST, alkaline phosphatase and immunoglobulins of the IgE, IgG and IgM classes in the blood serum of rats did not reveal statistically significant differences in comparison with the control data.

3. On the basis of a comparative histomorphological study of organs and tissues of control and experimental animals, it can be concluded that no necrosis, hemorrhages, dystrophic changes were observed in micropreparations of the stomach, liver, heart, lungs, kidneys of the spleen, regardless of the doses of the phytopreparation.

4. It was also proved that the studied drug in the studied doses does not have a negative effect on the bioelectric activity of the heart and on the contraction of the respiratory system. Phytopreparation at elevated pressure briefly lowers blood pressure.

5. Studies have shown that the studied liquid extract and its dealcoholized form do not have a local irritating and cumulative effect, since no specific changes were revealed during a visual macroscopic examination of the skin of animals in comparison with the control ones.

6. It was found that the phytopreparation has a pronounced hypoglycemic effect in laboratory rats with hyperglycemia.

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