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EVALUATION OF THE EFFECTIVENESS OF A DRUG OBTAINED ON THE BASIS OF VACCINIUM MYRTILLUS L., GALEGA OFFICINALIS. L. IN A MODEL OF HYPERGLYCEMIA TYPE OF DIABETES MELLITUS

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Relevance. Diabetes mellitus is one of the global medical and social problems in the healthcare system today. According to the International Diabetes Federation (IDF), in 2019 there were more than 425 million patients with type II diabetes worldwide [1,2,3,4].

The medical and social significance of diabetes is explained by 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 [5,6,7,8,9].

Pharmacotoxicological studies of drugs used for the treatment of diabetes mellitus and its complications, which affect metabolic processes in different ways, are carried out in the world [10,11,12,13]. Special attention is paid to the development of biologically active drugs based on local medicinal plants and providing the population with inexpensive local medicines. 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 most effective of them is blueberries and medicinal Galega. The studied phytopreparation contains blueberries and Galega Officinalis in its composition [14, 15,16,17,18,19,20].

In this regard, it is necessary to evaluate the pharmaco-toxicological effectiveness of the phytopreparation obtained on the basis of medicinal plant extracts Vaccinium myrtillus l.and galega officinalis l.

Thus, preclinical studies of a new antidiabetic phytopreparation were conducted for the first time and in the future it will be a very popular and urgent task to introduce it into clinical practice.

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

Materials and methods of research. The study of acute toxicity of the new antidiabetic drug was carried out on 20 mature white male rats with an initial body weight of 160-183 gr. exposed to intragastric doses of 500, 550, 600 and 650 mg/kg. Animals were intragastrically injected with 3.0 ml / 100 g of body weight. The chronic toxicity of the phytopreparation was studied under conditions of intragastric exposure in white rats at doses of 6, 60 and 120 mg/kg for 30 days. In the experiment, 24 white male rats with an initial body weight of 162-180 g were used. The effects of the new drug on blood pressure and respiration are studied in acute opitis on 4 cats and 2 rabbits weighing 2.5-3.5 kg of both sexes. The experiment was carried out under urethane anesthesia. Urethane was administered intraperitoneal at a dose of 1-1.2 g/kg. Arterial pressure was recorded on an electrokymograph tape from the common carotid artery through a system of polyethylene tubes with a mercury Ludwig manometer. The system was filled with a 5% solution of sodium citrate, 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 the Marei capsule connected to the trachea of the animal.

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

The study of the local irritant effect of the liquid extract of the new drug in the first series of experiments of the conjunctival test was performed on rats, guinea pigs and rabbits. In each experimental group there were 3-5 heads of animals. The liquid extract in various concentrations and in the form of evaporation in a dealcoholized form was applied 1-3 times to the conjunctival sac of the right eye. The right eye of guinea pigs and rabbits. The left eye was a control. The reaction of the conjunctiva to the substance in a concentration of 0.25-1.0% solution and a dealcoholized form in dilution 1/10 was evaluated by 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 phytopreparation on the skin. At the same time, pre-cut wool of 1cm ×1cm and 2cm×2 cm in the studied concentrations and dealcoholized form was lubricated for two weeks. 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 orally injected with a special metal probe with an olive into the first group of animals, and a dealcoholized form of the phytopreparation was injected into the second group. The third group was a control group. In the first 5 days, the studied phytopreparation was administered, respectively, 1 ml and 1.5 ml per animal weight.

The model of acute hyperglycemia was called according to the method described in the book by O. V. Remizov and T. L.Kuraev. In order to exclude the effect of food on the absorption of the test substance, feeding of animals was stopped 4-6 hours before the experiment. Prolonged fasting is undesirable due to the fact that in this case the severity of the hypoglycemic effect of the drug decreases. Experimental hyperglycemia in rats was caused by a single intraperitoneal injection of a hypertonic glucose solution at a dose of 4.5 g/kg. 30 minutes before the introduction of glucose, the test substances were administered orally using a probe in the form of a 10% aqueous solution. After 30, 60, 90 and 120 minutes, the blood glucose level was determined by the enzymatic method. Glucose determination was carried out in blood serum by the enzymatic method. On the model of acute hyperglycemia, the activity of a new phytopreparation was compared with a well–known hypoglycemic drug - domestic Glucaire (50 mg / kg). For this purpose, Phytodiabetol was used in doses of 6 and 60 mg / kg. The experiments were carried out on 24 mature white rats weighing 160-180 g.

The results of the study. 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 died- 1, receiving 600 mg/kg-2, receiving 650 mg/kg-4. Experienced animals reacted adequately to external stimuli. The visible mucous membranes are moist, pale pink in color, shiny and smooth in appearance, foci of baldness have not been detected.

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

The results of the experiments conducted to study the acute toxicity of Phytodiabetol showed that with intragastric single 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 phytopreparation on the dynamics of body weight changes in laboratory animals. Macroscopic pathologic-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 Phytodiabetol in 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, body weight gain and hematological parameters (Table 1).

Table 1

Changes in hematolytic parameters of peripheral blood of rats under the influence of phytopreparation

Dose groups	Leikotsiyou, 10 9/l	Absolute content of tov lymphocytes, 10 9/l	Absolute content of a mixture of monocytes, basophils and eosonophils fishing, 10 9/l	Quantity of granules of the tov lot, 10 9/l	Hemoglobin lobin, g/l	Erythrocytes, g/l RBC	Hematocrit, % HCT	The average concentration of hemoglobin in the erythrocyte te, g/ l	Platelets you in absolute numbers, 10 9/l	Thrombocrit,%
Contact role	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 мг/кг	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 мг/кг	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 мг/кг	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 priming of animals. The study of the dynamics of ALT, AST, and alkaline phosphatase content in blood serum did not reveal statistically significant differences in experimental rats compared with control data. Data analysis peripheral blood parameters and indicators of alkaline phosphatase, trans-aminase enzymes (ALT, AST) in the blood serum of animals, it indicates that the phytopreparation in the studied doses does not have a significant effect on the tested parameters. That is, the indicators of alkaline phosphatase, transaminase enzymes (ALT, AST) the blood serum in experimental animals did not differ significantly from the control values. There were changes in the concentration of glucose in the blood of rats taking the test drug, especially in high concentrations (Table 2).

Table 2.

Changes in biochemical blood parameters of rats taking phytopreparation

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

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

As can be seen from Table 2, oral intake of 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 the activity of alkaline phosphatase, alanine and aspatrate aminotransferases indicates a low the toxicity of this drug.

The results of the effect of the studied phytopreparation on the content of immunoglobulins of the IgE, IgG, IgM classes 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 does not significantly affect the content of immunoglobulins of the IgE, IgG and IgM classes in serum rat blood.

Table 3

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

Dietary SUPPLEMENT	The dose of the drug mg / kg	IgE concentration, IU/ml	IgG concentration, mg/ml	IgM concentration, mg/ml
«Phytodiabeton»	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	-	3,0±0,1	4,1±0,6	0,14±0,02

In a pathoanatomic study conducted 30 days after intragastric exposure to phytopreparation, at doses of 6, 60 and 120 mg/kg, it was found that in rats of the experimental groups, the appearance, size and macroscopic structure of internal organs did not visually differ from the control ones. These results confirm that the studied substances do not have toxic properties. All the animals had the right physique, neat appearance, shiny coat. The visible mucous membranes are moist, pale pink in color, shiny and smooth in appearance. The males' external genitalia had no visible deformities 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 Phytodiabet, regardless of the dose of exposure, revealed a similar picture. The liver capsule in experimental animals is not thickened, it contains longitudinally oriented bundles of collagen fibers. The liver parenchyma

is formed by classical hepatic lobules consisting of hepatic plates or beams radially oriented to the central vein. Hepatocytes are polygonal in shape, with a centrally located nucleus
(Fig.1,2).

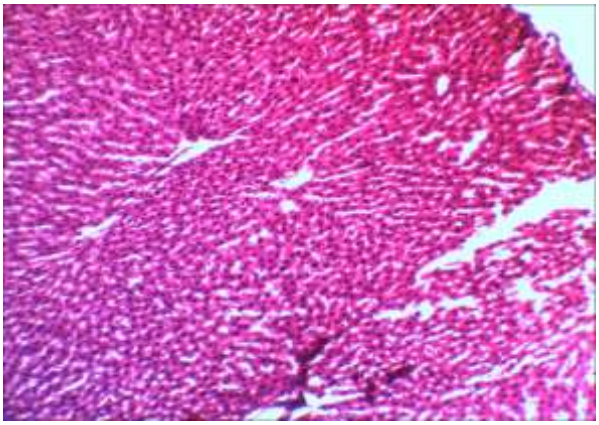


Fig. 1. Rat liver after intraventricular exposure. The structures are not broken, there are no dystrophic changes. there are no changes. Coloring GE. About. 10x10.

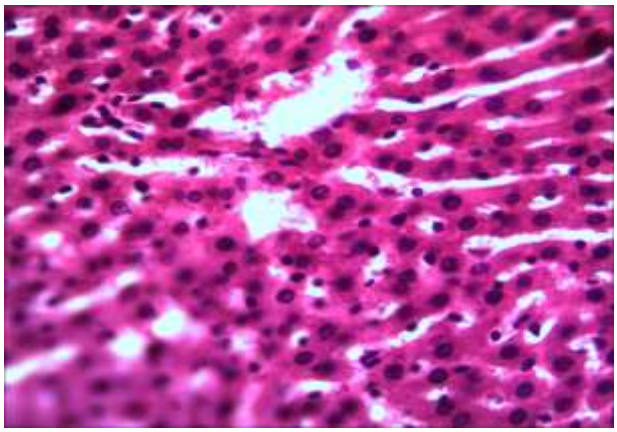


Fig. 2 . Rat liver after intraventricular exposure. Central Vienna. The structures are not broken, there are no dystrophic changes. Color GE. About. 10x40.

Stomach – in the esophageal and glandular part of the stomach, regardless of the dose of exposure, dystrophic changes were not detected (Fig.3, 4).

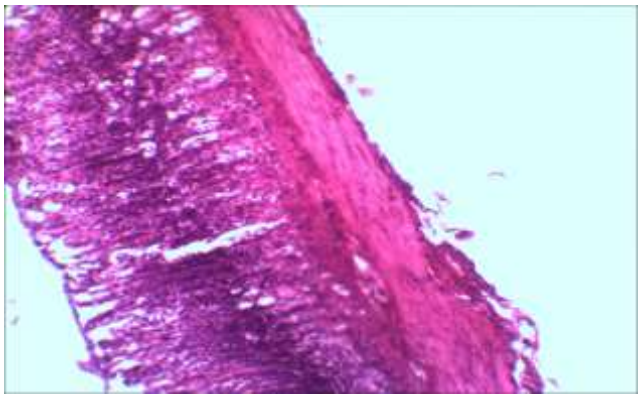


Fig.3. The stomach is the glandular part. Mucous membrane, submucosa, muscle membrane. The structures are not broken, there are no dystrophic changes. Coloring GE. About. 10x10.

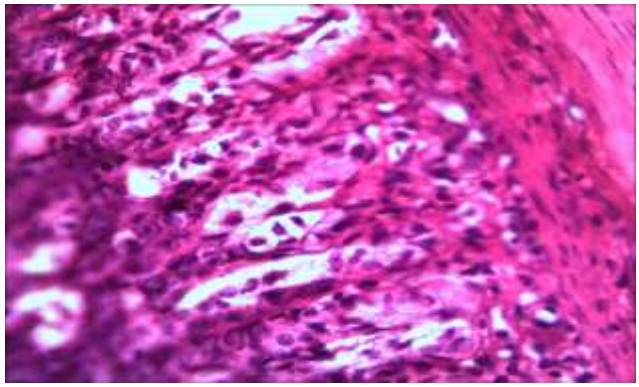


Fig.4. The stomach is the glandular part. glands. Main cells, parietal cells. The structures are not broken, there are no dystrophic changes. Color GE. About. 10x40.

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

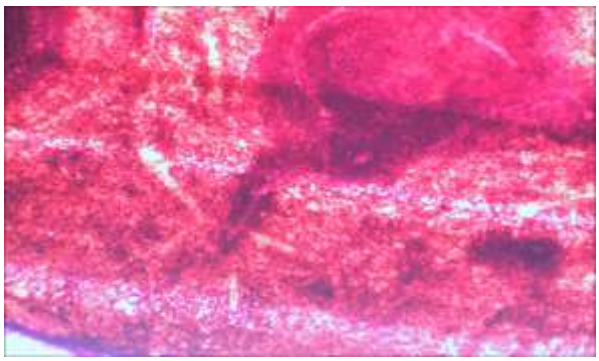


Fig. 5. The spleen. Lymphoid follicle, red pulp. The structures are not broken, there are no dystrophic changes. Coloring GE. About. 10x10.

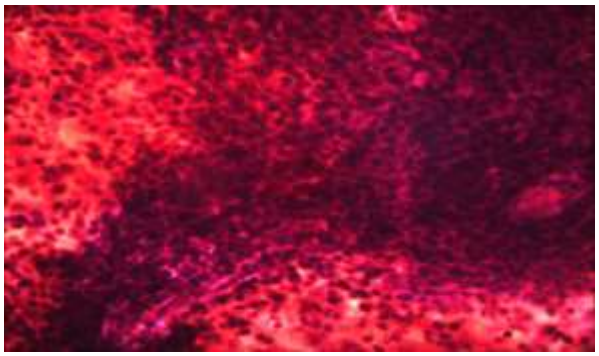


Fig.6. The spleen.The central artery of the foliculus. The structures are not broken, there are no dystrophic changes. Color GE. About. 10x40.

Lungs. No changes are detected in the lung tissue (Fig. 7,8).

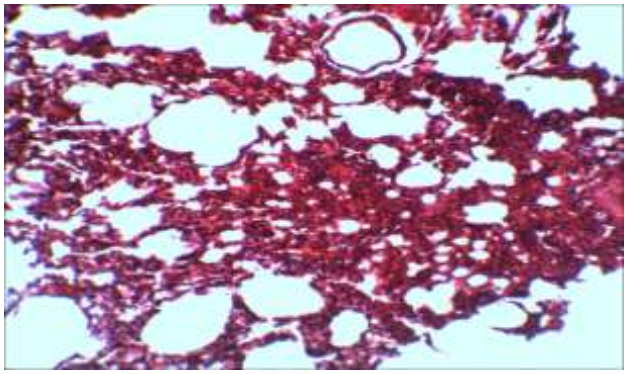


Fig. 7. The lung.Bronchioles, alveoli. Structures are not broken, dystrophic there are no changes. Coloring GE. About. 10x10.

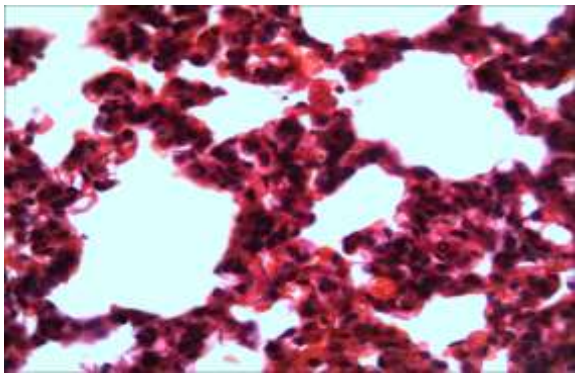


Fig.8. Lung of the alveoli. The structures are not broken, there are no dystrophic changes. Color GE. About. 10x40.

Heart. No changes are detected in the heart muscle tissue (Fig. 9.10).

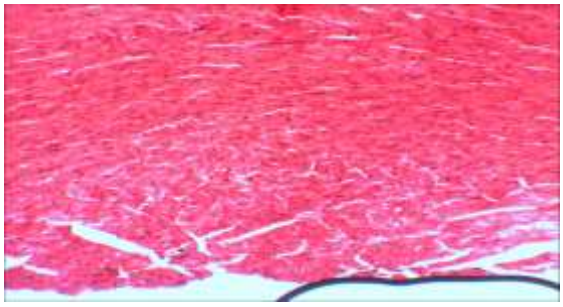


Fig.9. The heart. Myocardium. Structures are not they are broken, there are no dystrophic changes. Coloring GE. About. 10x10.

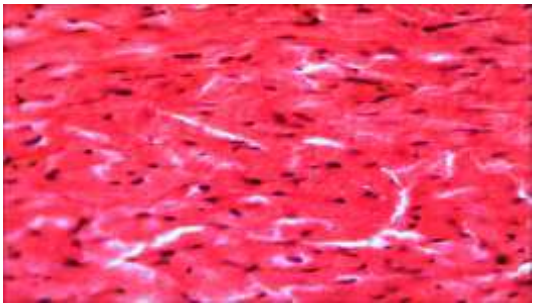
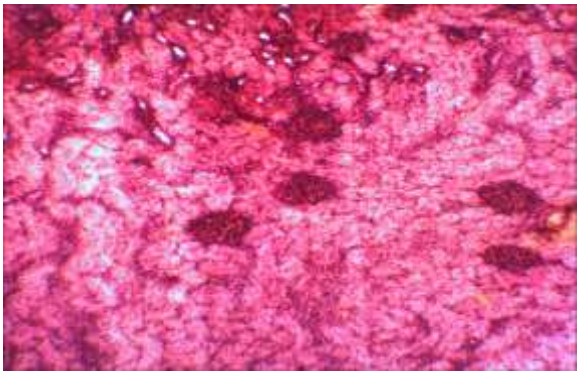


Fig.10. The heart.Cardiomyocytes. The structures are not broken, there are no dystrophic changes. Color GE. About. 10x40.

Kidneys. There are also no changes in the kidney tissue (Fig. 11-14).



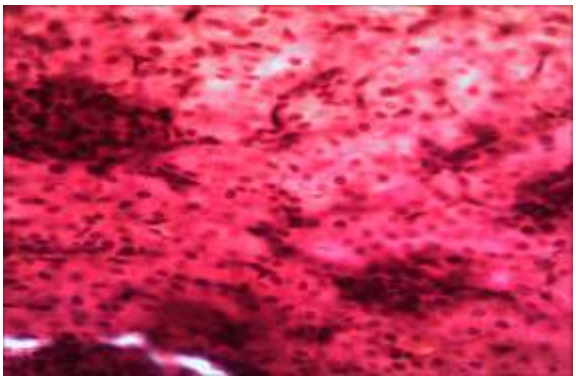
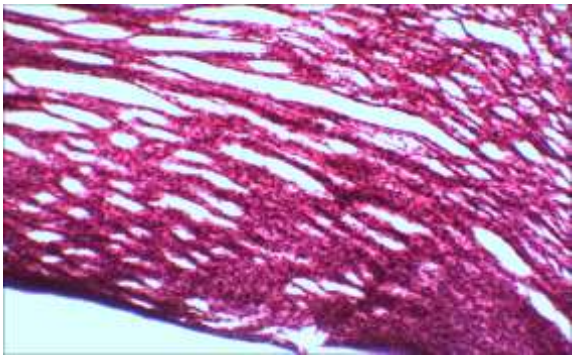


Fig. 11. Kidney cortical substance. Glomeruli, tubules.The structures are not broken, there are no dystrophic changes. Coloring GE. About. 10x10.	Fig.12. Kidney cortical substance. Glomerulus, tubules.The structures are not broken , there are no dystrophic changes. Color GE. About. 10x40.



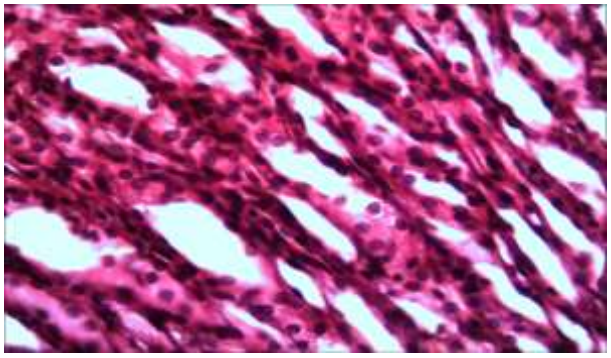


Fig. 13. Kidney medulla pyramid. The structures are not broken, there are no dystrophic changes. Coloring GE. About. 10x10.	Fig.14. Kidney medulla tubules. The structures are not broken, there are no dystrophic changes. Color GE. About. 10x40.

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

Based on a comparative histomorphological study of organs and tissues of control and experimental animals, it can be concluded that, regardless of the doses of the phytopreparation, necrosis, hemorrhage, and dystrophic changes were not observed in micro-preparations of the stomach, liver, heart, lungs, and kidneys of the spleen.

The data obtained by studying the phytopreparation for blood pressure and respiratory rate showed that it in doses of 5 and 10 ml / kg slightly reduced blood pressure (by 5.2% and 6.4%) and briefly extinguished the respiratory rate (by

2.7%). When a dose of 25 ml / kg is administered, it reduces blood pressure more significantly (by 18.3%), which lasted no more than 23-35 minutes. The effect of the phytopreparation on blood pressure was more pronounced at high baseline pressure.

Analyses of the bioelectric 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 heart rate, 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 atrial myocardium (P wave) and ventricles (QRS) was normal and there were no changes in the conducting system.

Studies have shown that the liquid extract under study and its dealcoholized form does not have a locally irritating effect, since no special changes were detected during visual macroscopic examination of animal skin compared to control ones. 14-day observation 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, it can be said that the studied phytopreparation in the concentrations studied does not have a locally 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 mass, and on the 11th-15th day of the experiment, 2.5 ml and 4.0 ml per mass, and in the next 5 days, respectively, 3 ml and 6 ml per animal mass. The control group received distilled water according to the same scheme and the dose of exchange. The condition of the animals was monitored visually, while the main attention was paid to the general condition, reactions to external stimuli, appetite and the mass of animals.

Experiments have shown that there were no significant differences in weight in both experimental and control groups of animals. The mucous membrane and the coat of all animals were unchanged. The animals enjoyed eating and drinking water. The respiratory rate in all groups of animals was the same, disorders from the gastrointestinal tract were not observed. When opening the animals on the 20th day of the experiment, a normal histomorphological picture of the internal organs was observed in all animals, no visual changes were detected from the vital internal organs. Hypoglycemic activity of the drug has also been proven.

Biochemical parameters of rat blood in an experimental model of hyperglycemic

Groups	Alanine aminotransferase activity, ALT	Alkaline phosphatase activity, ALP	Glucose, Glu	Total bilirubin, TBil	Direct bilirubin, DBil	Total protein, TR
	Ед/л (при 37^{0}C)		Ммоль/л			г/дл (при 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**
Phytodiabeton 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
Phytodiabeton 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
Phytodiabeton 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
Glusker 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

type of diabetes formation (n = 6, M ± m).

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

As can be seen from Tables 3, the concentration of glucose in the blood serum of animals of the control group with diabetes with high confidence (P< 0.0001) exceeds the concentration of glucose in the blood of animals of the intact control group, which indicates the effectiveness of the model of the hyperglycemic method of causing diabetes in experimental animals. "Phytodiabetol", as well as the reference drug "Glucair" in 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. Changes on the part of the enzyme alanine aminotransferase were not observed in experimental animals. The activity of the alkaline phosphatase enzyme in animals without drug therapy increased by one order of magnitude in this model, the activity of which decreased significantly (P< 0.05) to the norm of intact animals in all animals taking the studied drugs. In this model, the concentration of billirubin, both direct and general, increased twice 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 and Glucair.

Conclusions.

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

2. With its subchronic administration, it was revealed that within 30 days of 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, there were no statistically significant differences compared with the control data.

3. Based on a comparative histomorphological study of organs and tissues of control and experimental animals, it can be concluded that, regardless of the doses of the phytopreparation, necrosis, hemorrhage, and dystrophic changes were not observed in micro-preparations of the stomach, liver, heart, lungs, and kidneys of the spleen.

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 with high blood pressure reduces blood pressure for a short time.

5. Studies have shown that the liquid extract under study and its dealcoholized form does not have a locally irritating and cumulative effect, since no special changes were detected during visual macroscopic examination of animal skin compared to control ones.

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

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