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PHARMACO-TOXICOLOGICAL RESEARCH AND ESTABLISHMENT OF QUALITY STANDARDS FOR CAPSULES BASED ON THE ARTICHOKE OF KEY BARBARED IN UZBEKISTAN

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Abstract---*This work presents the results of pharmaco-toxicological studies and established quality standards for the preparation of 450 mg based on prickly artichoke. Pharmacological studies on the study of acute toxicity showed that the "LD50" of the studied preparation of 450 mg capsules on the basis of prickly artichoke was> 12500 mg / kg. The studied capsules at a dose of 1000 mg/kg had an equivalent choleretic effect with the drug comparison tablets "Chophytol" manufactured by Laboratories Roza-Phytopharma, France. A 3% aqueous solution of 450 mg capsules at a dose of 300 mg/kg enhanced the bile excretory function of rat liver during intoxication with carbon tetrachloride and had an equivalent hepatoprotective effect with the reference drug. Embryotoxic and teratogenic effects of the drug in doses of 300 mg/kg and 1500 mg/kg with the introduction of "per os" were not detected. Established quality standards for 450 mg capsules based on prickly artichoke. The drug is standardized in accordance with the requirements of regulatory documentation for the following indicators: description, authenticity, average weight, disintegration, heavy metals, microbiological purity, quantitative determination.*

Keywords---*prickly artichoke, acute toxicity, hepatoprotective activity, embryotoxicity, teratogenicity, choleretic activity, description, authenticity, average weight, disintegration, heavy metals, microbiological purity, quantitative determination.*

I. INTRODUCTION

Today in the world there are more than 10,000 medicinal plants that have healing properties used in both traditional and traditional medicine. A specific feature of plants is their ability to synthesize a variety of chemical compounds belonging to different classes. Having a biological effect on the body, such substances are able to stop or prevent various pathological conditions. Herbal remedies are used in medicine as much as there is the concept of treatment of diseases. Today, the study of the pharmacological activity of various medicinal plants, their extracts and individual natural compounds is given great importance. Modern science not only studies and carefully checks the experience of traditional medicine, but also replenishes the arsenal of medicinal herbs. Recently, there has been an annual increase in sales of modern medicines based on plant materials [1,2].

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Prickly artichoke (Cynara scolymus L.) is one of the oldest medicinal plants in the world used in medicine. It was known to the ancient Egyptians, Greeks and Romans as a medicinal plant that promotes digestion. Medicines based on prickly artichoke exhibit a wide range of pharmacological effects, such as hepatoprotective, choleretic, diuretic, hypoazotemic, hypocholesterolemic, anti-atherosclerotic, hypotensive, antitoxic, metabolic, normalizing digestion, metabolism [2]. Currently, the hepatoprotective properties of prickly artichoke are most in demand. This is due to an increase in the number of acute and chronic diseases of the liver and biliary tract, vital organs that carry out the biotransformation of endogenous toxins and xenobiotics; thereby cleansing the body of their harmful effects.

In the literature there is evidence of the successful use of these drugs in the treatment of urticaria, serum sickness, psoriasis, and eczema. Also, they are widely used for dyspeptic diseases caused by functional disorders of bile secretion, since these drugs can accelerate the breakdown of dietary fats, eliminate the feeling of heaviness in the stomach, nausea and abdominal pain. The mechanism that normalizes the effect of artichoke preparations on bile secretion is to increase the cholesterol content in the secreted bile. Extracts of this medicinal plant have the ability to dissolve existing deposits in the biliary tract. The extracts show the most pronounced effect in hyperlipidemia, which is closely associated with atherosclerosis. In addition, increased secretion of bile promotes the alkalization of food and, as a result, the protection of acid-sensitive intestinal mucosa. Along with these effects, artichoke drugs stimulate intestinal motility. It is important to note that the choleretic effect of these drugs is manifested by oral, parenteral and injection methods of administration [2, 3].

The purpose of this study is to conduct pharmaco-toxicological studies and establish quality standards for capsules based on prickly artichoke grown in Uzbekistan.

II. MATERIALS AND METHODS

The dosage form of the drug is 450 mg gelatin capsules. The active substance of the preparation is an aqueous dry extract of prickly artichoke 400 mg. Excipients microcrystalline cellulose 45.5 mg., Magnesium stearate or calcium stearate 4.5 mg.

The acute toxicity of the drug was studied in 72 white mice, weighing 18-22 g, mixed sex. The animals were divided into 6 groups, 6 animals each, which were injected once intragastrically (using an atraumatic metal probe) with a 25% aqueous solution of the contents of the capsule (dry extract of artichoke) and the drug for comparison of tablets Chophytol (Laboratories Roza - Phytopharma, series VN 1133 Suitable for 07/2015) in doses of 6250 mg/kg; 7500 mg/kg; 8750 mg/kg; 10000 mg/kg; 11250 mg/kg and 12500 mg/kg, respectively.

Animals were monitored hourly during the first day of the experiment, while survival rates during the experiment, general condition, possible convulsions, and death were used as indicators of the functional state of the animals. Then, daily, for 2 weeks, in the animals of both groups, the general condition and activity of the animals was monitored, and behavioral reactions were taken into account. All experimental animals were kept in the same conditions and on a common diet with free access to water and food [3, 4].

The choleretic activity of the capsules was performed on sexually mature male mice, weighing 19 - 20 g. Animals on the eve of the experiment were left without food with free access to water. 60, 120 and 180 minutes before decapitation, the animals were intragastrically (using an atraumatic metal probe) 7% Cinaron bio solution in a dose of 1000 mg/kg (0.3 ml) was administered. Animals were divided into groups of 6 mice for each observation period and dose. Then, the animals opened the abdominal cavity, exposed the liver, bandaged the bile ducts distal and proximal from the gallbladder with a thread, cut off the gallbladder and weighed on a torsion balance. About the choleretic effect of the extract was

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judged by the difference in the mass of the gallbladder of the control and experimental animals. The cholagogue activity of “Cinaron bio” 7%, at a dose of 1000 mg/kg (0.3 ml) was compared with the choleretic drugs “Chophytol” 7%, at a dose of 1000 mg/kg (0.3 ml) and “Cinarix” 7% at a dose of 1000 mg/kg (0.3 ml) [5, 6].

Statistical calculations were performed using the unpaired student criterion.

The hepatoprotective activity of the drug was studied in 24 sexually mature rats weighing 180 - 240 g by the method of liver intoxication with carbon tetrachloride [5, 6]. Toxic liver damage CCl4 is accompanied by a sharp change in the structure of the liver with a predominant pattern of fatty degeneration of hepatocytes, as well as a decrease in the synthesis of bile acids and cholestasis.

For the experiment, rats were divided into 4 groups of 6 animals each:

Group 1 - intact (healthy) animals;

Group 2 (control) - animals with a picture of toxic hepatitis;

Group 3 (experience) - animals treated with CCl4 + 3% aqueous solution of the drug "Cinaron bio" at a dose of 300 mg / kg;

4 group (experience) - animals treated with CCl4 + 300 mg / kg of the drug «Chophytol”

To reproduce the picture of toxic liver damage, CCl4 in the form of a 50% oil solution was administered intragastrically for 2 days at a dose of 0.3 ml/100 g. Compared preparations were administered intragastrically to experimental groups of rats at a dose of 300 mg/kg of animal weight 2 hours before CCl4 intoxication. On day 3, the compared animals were injected with experimental preparations and after 3 hours the exocrine activity of the liver in rats was determined. Control rats not receiving CCl4 were anesthetized with sodium ethamine at a dose of 40 mg/kg intraperitoneally. In animals that reproduced toxic hepatitis, anesthesia with ethanol sodium was carried out at a dose of 30-35 mg/kg intraperitoneally, since in case of CCl4 hepatitis the detoxification function of the liver is inhibited. Then the abdominal cavity was opened, the common bile duct was isolated and cannulated. Bile was collected in hourly portions for 4 hours and its total volume was determined. At the same time, its main ingredients bilirubin, cholesterol and bile acids were determined in bile [5, 6].

The study of embryotoxicity and teratogenicity of the drug was carried out on 60 pregnant female white rats weighing 160.0-180.0 g and newborn fetuses from mothers who were injected with the studied drug [4]. Experimental animals were kept under normal vivarium conditions at 20–25 ° C. Embryotoxic, teratogenic effects of drugs depend on their chemical structure, ability to penetrate the placenta, the rate of their removal from the mother's body and the dose of the substance. Doses of the test drug (capsule content) were calculated per unit body weight of the animal, using the maximum (1500 mg/kg) at a concentration of 5% and therapeutic (300 mg/kg) at a concentration of 3%. The test drug was administered “per os” once a day from 1 to 19 days of pregnancy, covering the periods of implantation, placentation, organogenesis and fetal growth-development. The control was a group of animals kept in identical conditions and treated with saline. During pregnancy, experimental animals received the drug at the maximum and therapeutic dose. To continue the analysis, part of the embryos extracted from the uterine cavity were immersed in Buena liquid to examine the development of internal organs, part of the embryos were immersed in 96 ° alcohol, which were refreshed every 2 days for fixation for 7 days. From a liquid containing fruits, within 2 weeks, the formation and condition of the organs was checked according to the method of J. Wilson in the modification of I. R. Barylyak. In the last series, the Dawson method modified by A. P. Dyban was used for analysis, formation and development of the skeletal system [7].

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Quality standards for the study drug were set in accordance with the requirements of the Global Fund XI [2,8] for the following indicators: description, authenticity, average weight, disintegration, heavy metals, microbiological purity, quantitative determination. Composition per 1 capsule: dry extract of prickly artichoke - 400 mg, microcrystalline cellulose - 45.5 mg, magnesium stearate or calcium stearate - 4.5 mg. 450 mg capsules based on prickly artichoke are hard gelatin capsules filled with brown powder with a characteristic odor. Authentication was carried out by qualitative reactions to the main active substances, as the sum of hydroxycinnamic acids. The authenticity of the amount of hydroxycinnamic acids was established by the manifestation of blue fluorissence under UV light. About 0.4 g of the contents of the capsules was dissolved in 10 ml of hot purified water and mixed thoroughly. The resulting solution was applied using a capillary to the start line of chromatographic paper (15x15cm). Sample chromatographic paper was dried in air, placed in a chamber with 2% acetic acid, and chromatographed in an ascending manner. When the solvent front reached the edge of the chromatographic paper, it was removed, dried in a fume hood for 2 minutes. When looking at chromatographic paper under UV light, blue fluorescence appeared.

The average weight of the contents of the capsules and the deviations from the average weight of the capsules were evaluated according to the requirements of GF XI. The average weight of the contents of the capsules should be 450 mg ± 10% (table 6).

The decay times were also determined according to the requirements of GF XI. In this case, the capsules should disintegrate no more than 20 minutes. (table 6).

The determination of heavy metals was carried out by mass spectrometric method [8]. The analysis was performed on an ICP-MS instrument (inductively coupled plasma mass spectrometer) AT 7500a. Plasma power 1200 W, integration time 0.1 s, rotation speed of the peristaltic pump – 0.1 rpm. As a standard, a multi-element (27 component) standard solution was used with a target component content of 1.0 mg/L (table 6).

Tests for microbiological purity were carried out in accordance with the requirements of the Global Fund XI edition. 2, p. 193 "Methods of microbiological control of medicines" and Changes No. 2, dated 12.10.2005 category 3B. The results obtained for this indicator of the studied drug in five series corresponded to the specified requirements (table 7).

Quantification of the amount of hydroxycinnamic acids was carried out by the SF method. The contents of 10 capsules were mixed in a dry cup and 0.05 g (the so-called), dissolved in 50 ml of 50% ethanol, mixed thoroughly and filtered through a paper filter (solution A). 0.5 ml of filtrate A was placed in a flask with a capacity of 25 ml and the volume of the flask was adjusted with 50% ethyl alcohol to the mark. The optical density of the solution was measured at a wavelength of 329±2 nm. A comparison solution was 50% ethyl alcohol.

At the same time, the optical density of a solution of a working standard working standard sample (RSO) of chlorogenic acid was measured under similar conditions.

The content of the amount of hydroxycinnamic acids in percent, calculated on chlorogenic acid, was calculated by the formula:

$$X = \frac{Д_1 \cdot m_0 \cdot 50 \cdot 25 \cdot 0{,}5 \cdot C}{Д_0 \cdot m_1 \cdot 0{,}5 \cdot 25 \cdot 50} = \frac{Д_1 \cdot m_0 \cdot C}{Д_0 \cdot m_1}$$, где

D0 is the optical density of the OCR of chlorogenic acid;

D1 is the optical density of the test solution;

m0 — weight of a standard sample, g;

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m1 is a sample of the contents of the capsule, g;

C is the content of chlorogenic acid in CP, %.

In the course of the studies, the quantitative content of the sum of hydroxycinnamic acids in five series was established (table 8).

To prepare the OCO of chlorogenic acid, an exact weighed portion (0.01 g) of chlorogenic acid was transferred into a 50 ml flask and dissolved in 50% ethanol. 0.5 ml was taken from the solution into a 25 ml flask and the volume of the flask was adjusted to the mark with 50% ethyl alcohol.

III. RESULTS

The experiments showed that after a single intragastric administration of the studied drug and the comparison drug in doses from 6250 mg / kg to 12500 mg / kg, no visible changes were observed in the behavior and functional state of animals. No deaths were observed (table 1).

Table 1. Determination of acute toxicity (LD50) of capsule preparations based on prickly artichoke and “Chophytol”

№ p/p	The amount of drug administered, mg / kg	Total number of animals	The number of dead animals	(LD_{50}) drug
450 mg capsules based on prickly artichoke				
1	6250	6	0	>12500 mg/kg
2	7500	6	0	
3	8750	6	0	
4	10000	6	0	
5	11250	6	0	
6	12500	6	0	
“Chophytol”				
1	6250	6	0	>12500 mg/kg
2	7500	6	0	
3	8750	6	0	
4	10000	6	0	
5	11250	6	0	
6	12500	6	0	

“LD_{50}” of the test drug and the comparison drug> 12500 mg/kg;

Studies of specific activity showed that in animals after administration of a 7% solution of the studied drug (capsules of 450 mg of prickly artichoke) at a dose of 1000 mg/kg, a marked change in the mass of the gallbladder was observed. The mass of the gallbladder is 18.6±3.2 mg, that is, 34.8%. In the group of animals that received the study drug 120 minutes before decapitation, the mass of the gallbladder is 19.7±3.4 mg. Under the influence of the studied drug, the gallbladder mass in animals 180 minutes before decapitation was increased by 51.4% and amounted to 28.0±3.0 mg. When studying the effect of the drug “Chophytol” on the biliary function of the liver 60, 120 and 180 minutes before decapitation, the

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mass of the gallbladder was increased by 39.1%, 21.8 and 65.9%, which amounted to 19.2±1.2 mg; 20.7±2.4 mg and 30.7±2.2 mg, respectively (table 2).

Table 2. Change in gallbladder mass under the influence of 450 mg capsules based on the colophore preparation in comparison with the "Chophytol" preparation.

№ group	Name of the drug	The mass of the gallbladder, mg		
		after 60 min	after 120 min	after 180 min
1	Control group	1 3,8 ±1,5	17,0 ±1,8	18,5 ±2,4
2	450 mg capsules based on prickly artichoke 7 % solution, at a dose of 1000 mg/kg (0.3 ml)	18,6 ±3,2 34,8	19,7 ±3,4 15,9	28,0 ±3,0 51,4
3	"Chophytol" 7% solution, at a dose of 1000 mg/kg (0.3 ml)	19,2 ±1,2 39,1	20,7 ±2,4 21,8	30,7 ±2,2 65,9

Thus, a 7% solution of the studied drug at a dose of 1000 mg/kg significantly changed the mass of the gallbladder 60, 120 and 180 minutes after intragastric administration to white mice, which indicates its choleretic activity, i.e. its effect was equivalent with the drug "Chophytol".

The results of studies of hepatoprotective activity show that with liver tetrachloride intoxication, the bile excretory function of the liver is inhibited. So, if in intact (healthy) animals the volume of secreted bile per 1 hour averaged 0.57±0.09 ml, then in animals with hepatitis, the volume of bile per average 1 hour was 0.24±0.07 ml. The administration of an aqueous solution of the test drug to the animals stimulated bile formation already 1 hour after oral administration, i.e. on average 0.44±0.06 ml (table 3).

Table 3. The effect of the drug "Cinarone bio" on the biliary activity of the liver in comparison with the drug "Chophytol"

№	Group / drug	Time, hour/ml				Total ml	ml/100 g.
		1	2	3	4		
1	Intact(water for injection)	0,57±0,09	0,49±0,12	0,54±0,2	0,53±0,08	2,47±1,06	0,99±0,22
2	Control CCl_4	0,24±0,07	0,23±0,09	0,24±0,06	0,23±0,06	0,93±0,26	0,42±0,1 100%
3	CCl_4+ capsules of 450 mg prickly artichoke	0,44±0,06	0,4±0,02	0,36±0,12	0,36±0,06	1,56±0,2	0,72±0,07 167% P<0,05
4	CCl_4 + "Chophytol"	0,46±0,12	0,47±0,13	0,45±0,1	0,43±0,1	1,8±0,43	0,84±0,17 200% P<0,05

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The total amount of bile secreted in 4 hours in animals receiving an aqueous solution of the test drug at a dose of 300 mg / kg was 1.56±0.2 ml (167%).

When studying the choleretic effect of the drug “Chophytol” at a dose of 300 mg / kg, stimulation of the bile-forming function of the liver was observed, and after 1 hour, the volume of excreted bile averaged 0.46±0.12 ml with a control of 0.24±0.07 ml. The total amount of bile excreted within 4 hours was 1.8±0.43 ml (200%).

The test drug and the comparison drug accelerated the excretion of bile acids by 22 and 26%, bilirubin 19 and 26%, cholesterol 14 and 16%, respectively (table 4).

Table 4. The effect of 450 mg capsules on the basis of prickly artichoke on the speed and biochemical composition of bile in white rats in comparison with the Chophytol preparation (M±m; n=6)

Group / drug mg/kg	Total count bile for 4 hours, ml / 100g	The composition of bile, mg %		
		Bile acids	Bilirubin	Cholesterol
Intact	0,99±0,22	1812±10,3	26,5±1,2	54,6±1,6
Control	0,42±0,1	1015±15,4	18,3±0,8	46,1±0,8
450 mg capsules of prickly artichoke	0,72±0,07	1714±15,4*	24,3±0,8*	50,1±0,8*
“Chophytol”	0,84±0,17	1793±9,9*	25,2±0,7*	51,1±0,7*

Note: * - the difference is significant compared with the control at P <0.05

For biochemical analysis, a total bile sample was collected from all animals of the same group, and then the studied parameters were determined in the sample.

In order to study the embryotoxicity and teratogenicity of the drug on the 21-23th day of pregnancy, the uterine cavity was opened under experimental animals, and the state of internal organs (liver, lungs, heart, gastrointestinal tract, kidneys), the state of the bicornus, ovaries, and corpus luteum were visually examined. . Then, after resection of the lumen of the uterine horns, the sites of implantations, resorptions, the number of live and dead fetuses, the integrity of the placenta, their blood supply, the condition and content of amnion, amniotic fluid were examined. Removing the fruit, carefully using the binocular magnifier (MBS-10), umbilical cord, fetal mobility, external development of the skin, muscle layer were checked. At such an examination, attention was drawn to the presence of deformities, such as: cleft lip, cleft palate, anencephaly, hydrocephalus, and symptoms of genetic diseases like Down's disease. Further, the length of growth (cranio-caudal size), the formation of the external genitalia, deviations from the musculoskeletal system, in particular clubfoot, etc. were measured. Therefore, the analysis indicates the absence of teratogenic effect and normal development of the offspring.

Further, in the second series of experiments, where pregnant females received a therapeutic dose (300 mg/kg) of Cinaron Bio for 19 days, the periods of implantation, placentation, organogenesis, and growth-development in the prenatal period are covered. It is known that in the womb during the formation of internal organs, growth, development, carbohydrates, proteins, vitamins, and minerals are used most of all from metabolic products, which is why the test drug is enriched. In our studies, the daily feeding of pregnant females for 19 days contributed to the full development of large fruits in the amount of 7-9 litters per female, while the weight of the fetus was on average 6.5 g versus 4.6 g (control).

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Cranio-caudal sizes corresponded to the mass of the fruit. Correspondence of the number of yellow with live fruits proved the absence of pre- and post-implantation mortality. In the next series, a dose of 1,500 mg / kg of the study drug was tested. The effect of the maximum dose of the drug tended to increase weight with the birth of large-developed fruits, in the amount of 8-9 litters per female, weighing an average of 6.0 g. Cranio-caudal sizes corresponded to the weight of the fruits (table 5).

The experimental results show that the condition of the internal organs of the fetus, both in the control and from the mothers who received the drug in the maximum and therapeutic dose, is normal in the absence of pathological phenomena.

Table 5. Embryotoxic and teratogenic effects of the drug 450 mg capsules based on prickly artichoke

Date of introduction	The number of females, goals	The number of yellow bodies, g	The number of embryos who died after implantation, goals	The number of implantation sites	The number of live embryos, goals		The average mass of live fruit, gr	Cranio-caudal fruit size, cm
					Of which investigated			
					Wilson Method	Dawson Method		
1 to 19 days	60	95	-	95	25	30	-	-
Control	10	15	-	15			4,6	4,4-4,6
Maximum dose 1500 mg/kg	25	30	-	30			6,5	6,0-6,5
Therapeutic dose of 300 mg/kg	25	30	-	30			6,0	5,8-6,0

The last series of studies is devoted to the study of growth and development in the postnatal period, which takes into account the opening of the palpebral fissures (12-14 days), auricles, teething (6-8 days), the development of sucking, motor reflexes, the development of the muscular system, external genital organs, which according to our observations corresponded to the norm. In our experiments, no abnormal phenomena were found on the part of the skeletal-skeletal system.

The results of determining the average weight, disintegration time and heavy metals of 450 mg capsules based on artichoke correspond to the requirements of regulatory documentation (table 6).

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Table 6. The results of determining the average weight, disintegration time and heavy metal capsules of 450 mg of prickly artichoke

Capsule series	The average weight of the contents of the capsules and deviations from the average weight, mg ± 10%	The results of determining the decay time, min.	The results of the determination of heavy metals, mg/kg					
			Element	Content	Element	Content	Element	Content
1	450	16	Li	0,99	Ca	1490,00	Pb	0,50
2	449	18	Be	0,69	V	3,78	Bi	0,02
3	451	15	Na	1400,00	Cr	0,89	Ni	16,0
4	450	18	Mg	1700,00	Mn	2,00	Cu	8,30
5	450	17	K	8999,00	Fe	30,00	Cd	<0,2300

According to the results on the microbiological purity of the studied drug in five series, they met the specified requirements (table 7).

Table 7. The results of determining the microbiological purity of capsules of 450 mg of prickly artichoke

Indicators	Regulatory requirements	Analysis results
The total number of aerobic bacteria (in 1 g)	Must be no more than 10^5/1 gram (total)	Less than 10 CFU
The total number of yeast and molds (in 1 g)	Must be no more than 10^4/1 gram	10 CFU
Escherichiacoli (in 1 g or 1 ml)	Must be absent	Absent
Enterobacteria and other gram-negative bacteria	Must be no more than 103/1 gram	Absent
Salmonella (in 10 g or 10 ml)	Must be absent	Absent

According to the research results, the quantitative content of the amount of hydroxycinnamic acids in the preparation in terms of chlorogenic acid should be at least 5.5% (table 8).

Table 8. Metrological characteristics of the results of the quantitative determination of the amount of hydroxycinnamic acids in terms of chlorogenic acid

The optical	Found oxycinnamic	Metrological characteristics

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density, D	acids,%	
0,088	5,17	$\overline{X}= 7,122$ $S= 0,0501$ $S_{\overline{x}} = 0,0224$ $\Delta X= 0,128$ $\Delta\overline{X}= 0,057$ $\varepsilon= 1,79$ $\overline{\varepsilon}= 0,80$
0,099	7,11	
0,111	7,11	
0,122	7,17	
0,133	7,05	

IV. CONCLUSIONS

1. Pharmacological studies on the study of acute toxicity showed that the "LD_{50}" of the studied preparation of 450 mg capsules on the basis of prickly artichoke was >12500 mg/kg, according to the classification of toxicity of substances, with a single intragastric administration to 25 mice of a 25% aqueous solution of the drug was harmless.

2. The test capsules of 450 mg on the basis of prickly artichoke at a dose of 1000 mg / kg had an equivalent choleretic effect with the drug "Chophytol".

3. A 3% aqueous solution of the preparation of capsules of 450 mg at a dose of 300 mg / kg enhanced the bile excretory function of the liver of rats with carbon tetrachloride intoxication and had an equivalent hepatoprotective effect in comparison with the drug "Chophytol".

4. Thus, analyzes of studies of the preparation of 450 mg capsules on the basis of dry extract of prickly artichoke in doses of 300 mg/kg and 1500 mg/kg with the introduction of "per os" do not have embryotoxic and teratogenic effects.

5. Based on the experiments, quality standards for 450 mg capsules based on prickly artichoke were established. The drug is standardized in accordance with the requirements of regulatory documentation for the following indicators: description, authenticity, average weight, disintegration, heavy metals, microbiological purity, and quantitative determination.

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