# Pre-clinical study of the antiaterosclerotic drug firutas on pathomorphological changes in the organs of animals with long administration

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https://doi.org/10.5281/zenodo.5576506

**Abstract.** This article is devoted to the preclinical study of the anti-atherosclerotic drug firutas on pathomorphological changes in animal organs during prolonged administration. Preclinical study of the general toxicology of the drug "Firutas" showed that it belongs to the IV class of low-toxic compounds. The drug "Firutas" does not have a cumulative and locally irritating effect. With repeated intramuscular administration to mice and rats, it does not affect the behavior and weight dynamics of animals, does not have a toxic effect on the composition of peripheral blood, kidney and liver function, as well as on the pathomorphology of animal organs and tissues. All the above data allow us to conclude that the drug does not have a toxic effect on the body of animals.

## 1 Relevance

Atherosclerosis is a chronic lesion of the arteries caused by the proliferation of multiple dense nodular thickenings of the walls of the artery (plaques), narrowing its lumen and contributing to the formation of a blood clot, a thrombus, which can clog the vessel.

Atherosclerosis develops as a result of complex structural changes occurring in the intima (inner layer) and in the media (muscle layer) of the arteries, and it is associated with the accumulation of lipids and mucopolysaccharides in the blood vessels, the proliferation of connective tissue and the deposition of calcium. Cardiovascular disease, and this ischemic heart and brain disease, occlusive peripheral arterial disease, is the most common cause of morbidity, mortality and disability in the population of industrially developed countries [1,2,3,12]. Cardiovascular disease is the leading cause of death in the world. About 1/3 of the total number of deaths is due to this cause (17.9 million people per year).

The most important modifiable risk factors for cardiovascular disease are hypertension, overweight and dyslipoproteinemia. Arterial hypertension is widespread among the

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population (approximately 40% in the world) and causes about 9.4 million deaths per year


[5,6,7]. It is known that dyslipoproteinemias, in particular an increased level of total cholesterol and low-density lipoproteins, increase the risk of developing cardiovascular diseases and cardiovascular mortality [4,5,6,8,18]. At the same time, hypertriliciridemia has remained an ambiguous risk factor for cardiovascular diseases for many years. However, recently there has been information about the presence of an independent negative effect of an increased level of triglycerides on the development of diseases of the cardiovascular system [9,10]. And since hypertriglyceridemia is highly common (30% of the population in the United States, 29.2% in Russia), it can be assumed that it makes a significant contribution to the formation of the population risk of mortality [9, 10, 11].

Treatment of atherosclerosis is one of the urgent problems of modern medicine. Currently, for the prevention and treatment of atherosclerosis, there are a number of drugs belonging to different groups. However, with their long-term use, they cause a number of adverse side effects. In this regard, the search and study of new, more effective, less toxic hypolipidemic and antiatherosclerotic drugs is an urgent problem of modern pharmacology. Earlier, we found that the drug Firutas has a pronounced hypolipidemic, antiatherosclerotic effect and surpasses nicotinic acid in activity [1,3,4,5].

## 2 The purpose of preclinical study

Toxicological studies of the drug "Firutas" is to establish the nature and severity of its damaging effect on the body of experimental animals and assess its safety.

## 3 Research materials and methods

The general effect and toxicity of firutas was studied on white mice (weighing 18-20 g) and on rats (180-200 g) with oral and intra-abdominal administration at doses of 100, 500, 1000, 2000 and 3000 mg / kg 1-5% solution of the drug. To study the chronic toxicity of firtas, rats with an initial weight of 120-170 g were used. The experiments were carried out in the winter-spring season (December-May). The animals were divided into 3 groups. The drug was administered daily (7 times a week) orally for 180 days at doses of 100 mg / kg (therapeutic dose), 500 mg / kg (5 times higher than the therapeutic dose). The third group served as a control, where distilled water was introduced under similar conditions.

After the end of the experiment, rats of all groups were decapitated and sent for dissection and pathomorphological examination of internal organs [4,12,18].

During the experiment (in the initial state and after the completion of the experiment), the following was noted: the general condition was assessed by daily examination of the animals, the dynamics of body weight was weighed once a month, the behavior of rats was assessed by motor activity. All animals were subject to pathological examination at the end of the study. For microscopic examination were taken: the brain, heart, lungs with bronchi, stomach, pancreas, intestines, liver, spleen, kidneys, adrenal glands, uterus.

The experimental material was fixed in 10% neutral formalin, dehydrated in alcohols of ascending concentration, and embedded in paraffin. Paraffin sections with a thickness of 57 pm were obtained on a microtome, stained with hemotoxylin and eosin, and examined with a microscope. The study of the cumulative properties of firtas was carried out in experiments on rats weighing 100-200 g. The drug was administered orally daily for 14 days at doses of 1000 mg / kg and 1500 mg / kg (1/3 and 1/2 of the LD50, respectively). The control group of animals was injected with a solvent (distilled water) under similar experimental conditions.

To study the chronic toxicity of firtas, rats were used. The experiments were carried out on 24 rats of both sexes with an initial weight of 120-130 g.

The animals were divided into 3 groups. The drug was administered orally once daily for 180 days at doses of 100 mg / kg (therapeutic dose), 500 mg / kg (5 times higher than the therapeutic dose). The third group served as a control, where distilled water was introduced under similar conditions. Before and after the end of the experiment, hemoglobin, leukocytes, erythrocytes were determined in the peripheral blood, and the leukocyte formula was calculated. During the experiment (in the initial state and after the completion of the experiment), the following were noted:

- the general condition was assessed during the daily examination of the animals, the dynamics of body weight was determined by weighing the rats once a month, the behavior of the rats was loaned according to motor activity, hematological parameters
- the number of erythrocytes, leukocytes, platelets, the level of hemoglobin, the leukocyte formula was determined according to generally accepted methods.

## 4 Research results

The study of acute toxicity showed that firutas in doses of 100-2000 mg / kg with oral and intraperitoneal administration does not cause changes in the general condition of animals. With the introduction of the drug in doses of 2000-3000 mg / kg after 30-60 minutes, there was a noticeable decrease in the motor activity of the animals, while the reaction of mice and rats to external stimuli remained unchanged. On the next day, the activity of the animals was restored, no lethal outcome was observed. The average lethal dose could not be determined due to the large volume of the injected drug.

After a single injection, the animals were monitored for 14 days. The study of the cumulative properties of firutas showed that under the influence of firutas at the indicated doses, with the exception of slight inhibition, in the first 15-20 minutes after administration of the drug, no significant changes in the general condition and behavior were observed compared to control animals. In this case, in total, the animals received a dose 5-7 times higher than the maximum.

The death of animals was not noted. Consequently, firutas is not accumulated in the body of experimental animals when it is reintroduced. The study of the chronic toxicity of firutas showed that the drug was well tolerated after prolonged administration, i.e. rats receiving firutas at doses of 100 and 500 mg / kg for 180 days did not differ from control animals in appearance, behavior, reflex excitability, body weight, and hematological parameters. However, during the observation of the animals, it was shown that the weight of the animals receiving the drug Firutas increased steadily throughout the entire study period, both in the control and in the experimental groups (Table 1).

**Table 1.** The effect of the drug "Firutas" on the body weight of rats (M ± m).

| **Study timing** | **Control in grams** | **Firutas** | |
|---|---|---|---|
| | | **100mg / kg** | **500mg / kg** |
| Initial level | 126.2±9 | 127.2±6.6 | 133.7±18 |
| 30 days | 126.2±9 | 127.2±6.6 | 133.7±18 |
| 60 days | 133.2±7.5 | 138.2±9.6 | 140.8±9 |
| 90 days | 144.2±6.9 | 156.1±10.2 | 156.7±11.1 |
| 120days | 143.1±3 | 155.5±10.2 | 179.3±12 |
| 150days | 148.1±6 | 158.7±10.5 | 177.5±9 |
| 180days | 148.7±6 | 172.5±18 | 170.6±7.5 |

The results of the morphological studies of the blood showed that the picture of the peripheral blood of the experimental rats receiving firutas at doses of 100 and 500 mg / kg for 180 days did not differ significantly from the control animals. A slight increase in the number of leukocytes was found in both the experimental and control groups of animals (Table 2.).

**Table 2.** Peripheral blood parameters of rats treated with firutas in a chronic experiment (n=8), (M±m).

| Indicators | Control | | Firutas 100mg / kg | Firutas 500mg / kg |
|---|---|---|---|---|
| | Before introduction | After completion. Experience | | |
| Hemoglobin g / l | 103.1±1.2 | 102.8± 1.2 | 124.6±0.9 | 140±3 |
| Erythrocytes | 3.3 ±0.3 | 3.27±0.3 | 3.85±0.12 | 4.26±0.36 |
| Color show | 0.91±0.06 | 0.88±0.06 | 0.91±0.06 | 0.91±0.06 |
| Platelets | 187.8±0.6 | 187.2±0.6 | 187.6±0.3 | 187.7±0.3 |
| Leukocytes | 6.56±0.75 | 6.5±0.45 | 9.0±0.6 | 12.8±1.35 |
| Neutrophils: | | | | |
| Nuclear stick | 1.55±0.3 | 1.43±0.3 | 1.0±0.06 | 1.0±0.12 |
| Segment. nuclear | 25±0.9 | 24.7±1.2 | 38.7±1.2 | 23.5±0.9 |
| Eosinophils | 1.12±0.3 | 1.37±0.6 | 1.12±0.9 | 1.12±0.3 |
| Lymphocytes | 70.2±1.2 | 69.8±1.2 | 57.3±0.6 | 67.8±2.1 |
| Monocytes | 2.0±0.6 | 1.87±0.6 | 2.5±0.3 | 7.0±1.2 |
| ESR | 2.5±0.3 | 2.25±0.6 | 5.0±0.6 | 6.5±0.9 |

After the completion of the study of chronic toxicity, the animals were decapitated, a macroscopic examination of the internal organs was performed. On external examination, rats of the correct constitution, satisfactory nutrition. The coat is shiny, neat-looking, baldness foci are not detected. The group of rats treated with firutas at a dose of 100 mg / kg did not show significant changes in appearance. The teeth are preserved. Visible mucous membranes are pale and shiny. A group of rats that received Firutas at a dose of 500 mg / kg - in some rats, spot hair loss was noted. The teeth are preserved. Visible mucous membranes pale, shiny.

**The membranes of the brain** are thin, transparent. The substance of the brain is of normal density, the surface of the brain is smooth. On the frontal sections of the brain, gray and white matter are clearly distinguished.

**The thoracic and abdominal cavities were f**ree of effusion. The parietal and visceral layers of the pleura and peritoneum are thin, smooth.

**The stomach is of normal size and shape** filled with food contents. The mucous membrane (glandular part) of the stomach is folded, pinkish, shiny, without visible signs of irritation.

**Small intestine.** The mucous membrane of the small intestine is pale pink, shiny, smooth, without visible signs of irritation.

**Colon.** The mucous membrane of the large intestine is grayish, shiny, smooth, without visible signs of irritation.

**Liver.** The shape and size of the liver do not represent changes. The surface of the liver is smooth, homogeneous, dark red in color, the capsule is thin, transparent. Liver tissue in the section is full-blooded, moderately dense.

**The pancreas is flat.** Pale pink in color, lobed, of moderately dense consistency. The spleen is of normal shape, dark cherry color, of moderately dense consistency. The surface of the organ is smooth, the capsule is thin.

**Bud.** The size and shape of the kidneys are not changed. The surface of the kidneys is brownish, smooth, the capsule is thin, transparent, easily removable. On the section of the organ, the cortical and medulla are clearly distinguishable.

**The adrenal glands are rounded.** Pale yellow in color, with a smooth surface, moderately dense. The section clearly shows a dark colored medulla.

**The bladder.** Is filled with transparent urine, the mucous membrane of the bladder is smooth, shiny, pale in color. Consequently, no changes were noted during a macroscopic examination of the internal organs.

**Microscopy of internal organs of rats of the control group and the group that received firutas.**

**Brain**. In rats of the control group, the vessels of the cerebral part are filled with blood, not swollen, the connective tissue surrounding them, without signs of dystrophy. Gray and white matter are clearly defined, neurons without edema with clear boundaries, fibers and glia between them. The nuclei of the cells are large, light, with fine-grained chromatin, in some there are nucleoli. Cells are pyramidal or stellate with a large number of processes. The white matter is homogeneous, not loosened, without edema, dystrophy. The picture is correct. In the group of rats treated with firutas at doses of 100 and 500 mg / kg, no significant changes in the brain were observed. The brain, cerebellum are unchanged. Gray and white matter are clearly defined. There is no pericellular, perevascular edema. Neurons without signs of dystrophy.

**A heart.** In rats of the control group, the myocardium, pericardium, and endocardium are clearly defined. The endocardium is represented by flat cells lying in one layer on the swelling connective tissue. There are no signs of dystrophy. The myocardium is represented by closely related elongated cells with clear boundaries, having one or two nuclei. Seals (intercalated discs) are visible between the cells, the cytoplasm of the cells is striated (myofibrils). There are thin layers of connective tissue between the cells. Vessels are partly filled with blood, partly empty. Pericardium - connective tissue, moderately developed adipose tissue, blood vessels are free of blood. There are no signs of dystrophy. The picture resembles the norm. In the group of rats receiving firutas at doses of 100 mg / kg, no significant changes in the heart were observed. A group of rats treated with Firutas at doses of 500 mg / kg showed hyperemia, hemorrhage under the pericardium (possibly mechanical damage), proliferation of connective tissue layers.

**Lungs**. In rats of the control group, the bronchi and acini are clearly defined, the interstitium is made of thin layers of connective tissue and blood vessels. The bronchi are formed from the mucosa, submucosa, muscular, cartilaginous and outer membranes. The mucosa consists of a unilamellar multilayered epithelium, a lamina propria of connective tissue and a muscle lamina of smooth muscle cells. The submucosa contains glands located in the connective tissue, the muscular membrane is formed by smooth muscle cells. Under the muscles are cartilaginous plates made of hyaline cartilage. A connective tissue capsule is located outside. Acini are clearly defined. The alveolar epithelium is not swollen, the capillaries in the interalveolar space are not swollen. The picture is correct. The group of rats that received firutas at a dose of 100 mg / kg showed no changes in the interstitium, and at a dose of 500 mg / kg moderate interstitial lymphocytic infiltration, perebronchial lymphocytic infiltration was observed.

**Liver.** In rats of the control group, the capsule was not swollen, the beam structure was preserved. Central veins, vessels of the portal system are clearly defined. The sinusoids of the lobules are not dilated. The connective tissue layers in the portal system are thin, the triads are clearly defined. Hepatocytes with clear boundaries, homogeneous cytoplasm, with one or two rounded nuclei. Chromatin in the nuclei is fine-grained. Endothelium of sinusoids, Kupffer's cells are not swollen. In the marginal zone of 2 nuclear cells, the picture is normal. The group of rats treated with firutas at a dose of 100 mg / kg did not

change. The group of rats that received Firutas at a dose of 500 mg / kg showed moderate plethora of the portal tract. The girder structure is not disturbed. Hepatocytes are mono and binuclear with turbid swelling. The connective tissue layers are thin, there is some focal proliferation of the bile ducts.

**Kidneys.** In the control group of rats, the capsule is not swollen, the cortical and medulla are clearly defined, the glomeruli are without multicellularity, edema, and thickening of the capsule leaves. The proximal tubules are formed from cylindrical cells with rounded nuclei, turbid homogeneous cytoplasm. The nuclei are located in the basal part. The distal tubules are composed of cubic cells with light cytoplasm with round nuclei. Henle's loops are formed from small light-colored cells with small nuclei. The collecting ducts are composed of tall, cylindrical cells with light cytoplasm and rounded nuclei. The interstitium is formed by the connective tissue in which the vessels lie. The calyx cavity is lined with stratified transitional epithelium. The picture is correct. In some rats that received firutas at a dose of 100 mg / kg, it was noted: a kidney with focal plethora in the medulla, no changes were observed in the tubules. In rats treated with firutas at a dose of 500 mg / kg, moderate dystrophic changes in the proximal tubules are observed.

**Adrenal glands.** In the control group of rats, all layers of the cortex, cortex and medulla are clearly defined. The adrenal gland was unchanged. There are no signs of dystophia. In the groups of rats that received firutas at doses of 100 and 500 mg / kg, there were no significant changes in the adrenal gland.

**Spleen.** In the control group of rats, the capsule was not swollen. The boundaries between the red and white pulp are clear. In rats receiving firutas at a dose of 100 mg / kg, no changes were observed, and at a dose of 500 mg / kg, moderate follicular hyperplasia was observed.

**Pancreas**. In the control group of rats, the lobular structure is preserved. The cells of the islets of Langerhans are oxyphilically stained. The basophilic and oxyphilic zones of pancreatic cells are clearly identified. In rats treated with firutas at doses of 100 and 500 mg / kg, there are no significant changes in the pancreas.

**Gastrointestinal tract**. In the control group, the mucous membrane, submucosa, muscle, and serous membranes of the stomach are clearly defined. Fragments of the proventriculus and glandular part are determined. The mucous membrane of the proventriculus is lined with a stratified squamous non-keratinizing epithelium without signs of dystrophy. The lamina propria consists of loose fibrous connective tissue with a plexus of blood vessels without signs of dystrophy. The submucosa is formed by connective tissue, there are small vessels, some of which are filled with blood. The muscular membrane of smooth muscle cells of an elongated shape with one or two rod-shaped nuclei. Chromatin in the nuclei is finely dispersed, nucleoli are visible in some nuclei. The cells are located longitudinally and transversely, the mucous membrane is covered with a single-layer columnar epithelium without signs of dystrophy. The glandular part contains three types of glands, cardiac, fundic, and pyloric. They are located in the lamina propria, the mucous membrane, consisting of connective tissue. The mucous membrane is separated from the submucosa by a thin muscle plate formed from smooth muscle cells. The submucosa is formed by connective tissue, muscular from smooth muscle cells. The outer shell consists of connective tissue covered with unilamellar squamous epithelium. Cardiac glands - formed by short tubes containing prismatic cells with a nucleus in the basal part. The glands of the fundus of the stomach consist of three types of cells that form a tube: the main, the lining, and the accessory. The main cells are cubic, with a rounded nucleus, basophilic stained. The parietal cells are large, rounded with a small round nucleus, and oxyphilic stained. Additional cells are cylindrically located in the neck area, the nuclei are elongated, the cytoplasm is light. The picture is correct. There are no significant changes in the stomach of rats treated with firutas at doses of 100 and 500 mg / kg.

**Small intestine**. In rats of the control group, the mucous, submucosa, muscular, and outer membranes are clearly defined. Cylindrical mucosal epithelium with clear boundaries, rounded nuclei lie in the basal part, the cytoplasm is homogeneous. Goblet cells in sufficient quantity. There are no signs of dystrophy. In the lamina propria, there is connective tissue without infiltration and swelling. The muscularis mucosa is formed by smooth muscle cells. Submucosa, muscular and outer membranes without signs of dystrophy. The picture is correct. In rats taking firutas at a dose of 100 and 500 mg / kg, there are no significant changes in the small intestine.

**Colon**. In rats of the control group, the membranes are clearly defined. The crypt epithelium is cylindrical, cells with clear boundaries without swelling and without vacuolization. Lymphoid follicles are not hyperplastic, with clear boundaries. In the muscle layer, nerve plexuses are locally determined. The picture is correct. In rats taking firutas at a dose of 100 and 500 mg / kg, there were no significant changes in the large intestine.

**Uterus.** In rats of the control group, the membranes are clearly defined. The endometrial glands are simple, tubular, the epithelium without vacuolization in one row (state of rest), the endometrial vessels are not dilated, there is no plethora. The muscular and outer membrane showed no signs of dystrophy. There were no changes in rats treated with firutas at a dose of 100 and 500 mg / kg. The picture of peripheral blood in the study of chronic toxicity and body weight of animals are presented in previous publications [1]. Based on the data obtained, the following conclusions can be drawn.

## 5 Conclusions

1. The drug Firutas is low-toxic, when administered orally and intraperitoneally in doses of 1000-3000 mg / kg, it does not cause death of animals. LD50 - not established due to the large volume of the injected drug. Firutas does not accumulate in the body of experimental animals when it is reintroduced.
2. Rats receiving firutas at doses of 100 and 500 mg / kg for 180 days did not differ from control animals in appearance, behavior, reflex excitability, body weight, as well as hematological parameters.

Thus, the studies carried out have shown that the drug Firutas does not have a pronounced general toxic effect at therapeutic doses (100 mg / kg) in the body of experimental animals. Based on the data obtained, the following conclusion can be drawn that the drug Firutas is low-toxic, when administered orally and intraperitoneally at doses of 1000-3000 mg / kg, it does not cause death of animals. LD50 - not established due to the large volume of the injected drug.

Rats receiving firutas at doses of 100 and 500 mg / kg for 180 days did not differ from control animals in appearance, behavior, reflex excitability, and body weight. When examining the morphological preparations obtained from rats receiving firutas at a dose of loo mg / kg, the following morphological picture was observed: the brain, heart, liver, lungs, kidneys, adrenal glands, stomach, intestines, uterus without any significant changes. When examining the preparations obtained from rats receiving firutas at a dose of 500 mg / kg, the following morphological changes were observed: the brain, spleen, adrenal glands, lung, kidneys, stomach, intestines, uterus did not differ from the same organs of the control group. There were moderate degenerative changes in the liver.

Thus, the studies carried out have shown that the drug Firutas does not have a pronounced general toxic effect in therapeutic doses (100 mg / kg) in the body of experimental animals.

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