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# INVESTIGATION OF THE PROFILE OF DRY EXTRACTS OF IRIS HUNGARICA LEAVES AND RHIZOME TO DETERMINE THE CARDIOPROTECTIVE ACTIVITY IN THE RAT MODEL OF DOXORUBICIN CARDIOMYOPATHY

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*The search and creation of new cardioprotective drugs, especially of plant origin, with a prolonged effect and a minimum of side effects, is an urgent task to improve the prognosis of cardiovascular diseases, prevent the risk of developing complications, and increase the duration and quality of life of patients. Iris hungarica, from the Iridaceae family, has a long history of medicinal use in many countries of the world and is also recognized as a rich source of BAC.*

***The aim.*** *Study of the cardioprotective effect of dry extracts of leaves and rhizomes of Iris hungarica on the rat model of doxorubicin cardiomyopathy.*

***Materials and methods.*** *The research was conducted on 40 white outbred female rats, which were injected intraperitoneally with a solution of doxorubicin hydrochloride at a dose of 1 mg/kg, at the rate of 0.5 mL per 100 g of the animal's body weight, according to the scheme 2 times a week for 6 weeks. The cardiotoxic effect and protective properties of potassium orotate, dry extracts of leaves and rhizomes of steppe iris were evaluated by animal survival, determination of the relative heart mass ratio, functional state of the myocardium (ECG parameters) and biochemical parameters in blood serum and heart homogenate.*

***Results.*** *The analysis of indicators of the functional state of the conducting system of the heart shows that the 15-day use in the treatment of animals with doxorubicin cardiomyopathy of the dry extract of the leaves and rhizomes of Iris hungarica at a dose of 150 mg/kg demonstrates a cardioprotective effect at the initial stage. In the model of doxorubicin cardiomyopathy, the dry extracts of the leaves and rhizomes of steppe iris at a dose of 150 mg/kg showed a normalizing effect on biochemical parameters in blood serum and in heart homogenate and were not inferior to the action of the comparison drug potassium orotate at a dose of 100 mg/kg.*

*The dry extract of the rhizomes of steppe iris revealed the most pronounced effect on metabolism in cardiomyocytes. The cardioprotective activity of the dry extract of the rhizomes of the Iris hungarica is defined as a cardioprotector – of the anabolic and antioxidant type – those that accelerate the recovery of the heart muscle, protect the heart muscle from the action of free radicals, preventing premature aging and wear.*

***Conclusions.*** *In the model of doxorubicin cardiomyopathy in rats, indicators of the functional state of the conducting system of the heart of animals after the use in the treatment of animals of the dry extracts of the leaves and rhizomes of steppe iris in a dose of 150 mg/kg demonstrate a cardioprotective effect at the initial stage, a normalizing effect on biochemical indicators in the blood serum and in the homogenate heart and are not inferior to the comparison drug potassium orotate in a dose of 100 mg/kg.*

*The most pronounced effect of the dry extract of the rhizomes of Iris hungarica on the functional state of the myocardium and biochemical indicators in blood serum and heart homogenate was established.*

*The dry extract of the rhizomes of steppe iris is a promising herbal remedy for the creation of a new drug with cardioprotective properties*

***Keywords:*** *doxorubicin cardiomyopathy, cardioprotective activity, potassium orotate, Iris hungarica leaves dry extract, Iris hungarica rhizomes dry extract, phenolic compounds, HPLC*

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## 1. Introduction

Cardiovascular diseases (CVD) are a significant medical and social problem, as they occupy the first place in the structure of morbidity and mortality. Of special importance for modern pharmacotherapy is the effect of cardioprotective drugs on the processes of inhibition of ionic, electrophysiological, hemodynamic and morphological remodelling [1, 2].

The creation of new drugs is relevant, as is the need for modern innovations for the prevention and treatment of acute coronary catastrophes, as well as the importance of fundamental research modeling the endogenous potential of the cardiovascular system [3].

The mechanism of action of cardioprotective drugs is diverse. In the absence of hypoxia, cardiomyocytes "get" ATP due to the breakdown of acetyl-CoA in the Krebs

cycle, where the main source of energy is glucose and free fatty acids (FFA). With adequate blood supply to the myocardium, 60–90 % of acetyl-CoA is formed due to the oxidation of free fatty acids (FFA), and the remaining 10–40 % – due to the decarboxylation of pyruvic acid (PVA). Half of the PVA inside the cell is formed due to glycolysis, and the other half is from lactate, which enters the cell from the blood. Compared to glycolysis, FFA catabolism requires a large amount of oxygen for the synthesis of an equivalent number of ATP [4].

With a sufficient supply of oxygen to the cell, the glucose and fatty acid energy supply systems are in a state of dynamic equilibrium. In conditions of hypoxia, there is insufficient oxygen for the oxidation of fatty acids. As a result of this, there is an accumulation of underoxidized activated forms of fatty acids (acylcarnitine, acyl-CoA) in the mitochondria, which can block adenine nucleotide translocase, which is accompanied by inhibition of the transport of ATP generated in the mitochondria to the cytosol and damage to the cell membrane [5].

Therefore, it is possible to improve the energy status due to increasing the efficiency of the use of deficient oxygen by mitochondria by preventing the uncoupling of oxidation and phosphorylation, stabilization of mitochondrial membranes, weakening of inhibition of Krebs cycle reactions; restoration of lost components of the respiratory chain; formation of artificial redox systems that shunt the respiratory chain overloaded with electrons; economizing the use of oxygen and reducing the oxygen demand of tissues by weakening the respiratory control in mitochondria, or inhibiting the ways of its consumption; an increase in the formation of ATP in the process of glycolysis without an increase in lactate production, a decrease in the consumption of ATP by the cell for processes that do not determine emergency life support in critical situations; introduction of high-energy compounds into the body [4, 5].

Cardioprotectors are conditionally divided into direct and indirect. Direct cardioprotectors have a local effect (stabilization of membranes, influence on metabolism in cardiomyocytes, vasodilator effect) and central (regulation of vascular tone due to influence on CNS structures). Indirect cardioprotectors reduce the load on the myocardium and reduce or prevent heart muscle dysfunction [5, 6].

Therefore, the search and creation of new cardioprotective drugs, especially of plant origin, with a prolonged effect and a minimum of side effects, is an urgent task to improve the prognosis of CVD, prevent the risk of developing complications, and increase the duration and quality of life of patients.

Steppe iris (*Iris hungarica*) is a perennial rhizome plant from the *Iridaceae* family, which is widely grown in various European countries, including Ukraine. The country's wide raw material base makes the plant promising for pharmaceutical and medical use. Species of the genus Iris have a long history of traditional use in medicine in various countries of the world in the treatment of cancer, inflammation, and bacterial and viral infections [7]. Already, modern pharmacological studies show a good diuretic, choleretic, hepatoprotective, antimicrobial, anticancer effect, etc. [8]. The leaves and rhizomes of various types of irises contain mainly phenolic compounds (flavonoids, isoflavonoids, xanthones, hydroxycinnamic acids, tannins) [7], amino acids, carboxylic acids, terpenoids, which are biologically active components and determine the presence of the above pharmacological actions. However, there are currently no experimental articles on the cardioprotective effect of iris species that would confirm this use of irises in traditional medicine.

The aim of this study was to study the cardioprotective effect of dry aqueous extracts of leaves and rhizomes of *Iris hungarica* on the model of doxorubicin cardiomyopathy in rats.

**2. Research planning (methodology).**

The experiment involved the selection and study of the profile of dry extracts of leaves and rhizomes of Iris hungarica to establish cardioprotective properties on the model of doxorubicin cardiomyopathy in rats. All this will allow to determine the mechanism of action of dry extracts of Iris hungarica for the purpose of prevention and treatment of acute coronary catastrophes (Fig. 1).

The main criteria for the cardioprotective effect of a drug with metabolic activity include the presence of pronounced anti-ischemic effectiveness (restriction of the size of necrosis in myocardial infarction) and the absence of a hemodynamic effect, impact on heart rate (HR), myocardial contractility, blood pressure and other parameters [1, 4]. Plants of the genus Iris contain phenolic compounds, mainly flavonoids and isoflavonoids, which exhibit pronounced cardioprotective effects [9].

Considering the successful cultivation of steppe iris and the availability of a raw material base in Ukraine, the object of the study was the leaves and rhizomes of *Iris hungarica* for obtaining dry extracts and determining their cardioprotective properties.

To obtain dry extracts from plant raw materials, the traditional method of extracting plant raw materials with heating followed by filtration and evaporation was chosen. To determine the chemical composition of the obtained extracts, the method of High-Performance Liquid Chromatography (HPLC) was used, which is the optimal method for the analysis of biologically active components of complex plant substances [10].

To carry out a pharmacological study of the cardioprotective effect of dry extracts of leaves and rhizomes of steppe iris, the scientifically based: experimental model of doxorubicin cardiomyopathy and methods of determining the functional state of the myocardium and biochemical indicators in blood serum and heart homogenate were applied, according to generally accepted methods, as well as methods of statistical analysis of the research results.

Doxorubicin is one of the most effective antitumor antibiotics of the anthracycline series, and it is widely used in the treatment of oncological and haematological diseases. Doxorubicin causes serious side effects, and the heart is exposed to toxic effects, which significantly limits the use of this chemotherapeutic agent in clinical practice. It is believed that one of the main reasons for the toxic effect of doxorubicin on the myocardium is its ability to induce oxidative stress and disrupt metabolic pro-

cesses, including the regulatory effect of natural metabolites on cellular functions, which are necessary for the normal functioning of the myocardium [11, 12].

During the planning of the experiment, such characteristics of animals as age, sex, and body weight were considered to form experimental groups.

During the modelling of experimental cardiomyopathy, the possible risk of animal death due to the cytotoxic effect of doxorubicin on cardiomyocytes was considered [13].

After the reproduction of the experimental model of doxorubicin cardiomyopathy, starting from the 15th day of the experiment, the comparison drug and experimental drugs were used in the treatment.

According to methodological recommendations, after the reproduction of cardiomyopathy, animal survival, relative heart weight ratio, functional state of the myocardium (ECG parameters) and biochemical parameters in blood serum and heart homogenate were determined [14].

The evaluation of the effect of dry extracts of leaves and rhizomes of *Iris hungarica* was carried out considering the characteristics of the animals and, in comparison, with the intact control and control pathology, the comparison drug potassium orotate, using statistical analysis of the research results.

**3. Materials and methods**

*Plant material.* For research, rhizomes and leaves of steppe iris (*Iris hungarica* West et Kit., Iridaceae) were collected in the spring of 2019 in the M. M. Hryshko National Botanical Garden of the National Academy of Sciences of Ukraine (Kyiv, Ukraine). The raw material was dried to an air-dry state and crushed to a particle size of 2–3 mm for analysis.

*Obtaining dry extracts for biological analysis.* To substantiate the choice of the extractant, the extractive substances in the raw materials were determined according to the SPhU method 1 ed., Add. 1 [15], using distilled water, 30 %, 50 %, 70 %, 96 % ethyl alcohol as extractants. According to the results, it was determined that the optimal extractant is ethanol (70 % v/v) and purified water (Table 1).

*The chromatographic profile* of the obtained extracts was determined by HPLC according to the method [10]. The main conditions of the study are as follows: ACE C18 chromatographic column (250×4.6 mm, 5.0 μm; Pennsylvania, USA), flow rate – 1 ml/min, column temperature – 25 °C; the mobile phase included two solvents, 0.1 % acetic acid solution (A) and acetonitrile (B). Scheme of passage of the mobile phase through the chromatographic column: 0–8 min, 5–15 % B; 8–30 min, 15–20 % B; 30–48 min, 20–40 % B; 48–58 min, 40–50 % B; 58–65 min, 50 %; 65–66 min, 50–95 % B. Identification of components was carried out by comparing the retention time (*Rt*), peaks of UV spectra, mass spectra in the investigated samples of extracts of leaves and rhizomes of Hungarian iris with indicators of standards of phenolic compounds (chlorogenic acid, ferulic acid, cinnamic acid, mangiferin, isoorientin, astragalin, nigricin-4′-O-β-D-glucoside, genistein-7-D-glucoside, iristectorigenin B, nigricin, irigenin, 5,6-dihydroxy-7,8,3′,5′ -tetramethoxyisoflavone).

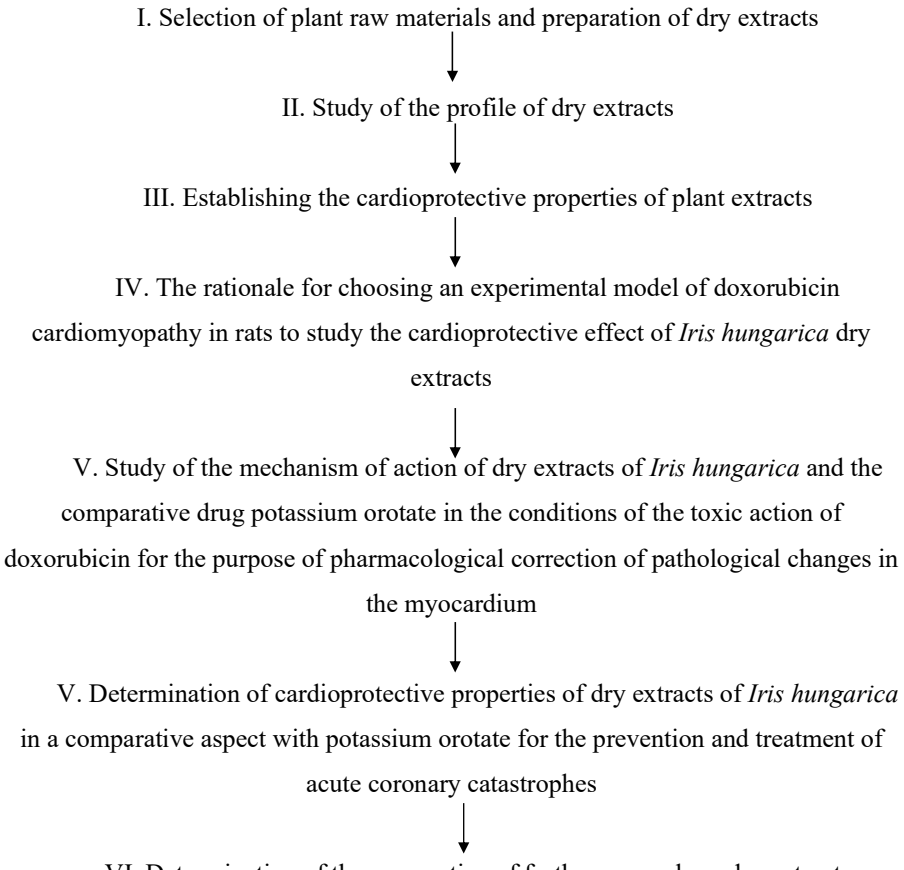



Fig. 1. Stages of conducting a study to determine the cardioprotective activity of dry extracts of *Iris hungarica*

The research protocol is consistent with bioethical norms and corresponds to the "General Ethical Principles of Animal Experiments" (Ukraine, 2001), and also does not contradict the provisions of the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes" (Strasbourg, 1986, with as amended in 1998) and Law of Ukraine No. 3447-IV dated 21.02.2006 with amendments "On the protection of animals from cruel treatment", "Order of the Ministry of Education and

Science, Youth and Sports of Ukraine No. 249 dated 01.03.2012 "Procedure carrying out experiments and experiments on animals by scientific institutions" [14]. The draft plan for the preclinical study of pharmacological properties of dry aqueous extracts of steppe iris leaves and rhizomes was approved by the bioethics committee of the NUPh (protocol No. A1 of 2020).

The animals were kept in the vivarium of the Central Research Laboratory of the National Pharmaceutical University, which is certified by the SE "SEC of the Ministry of Health of Ukraine" as a base for research in experimental pharmacology in accordance with the standards of sanitary norms and on the necessary food ration.

Preclinical studies of the cardioprotective activity of dry aqueous extracts of leaves and rhizomes of steppe iris were conducted in 2020 on 40 purebred female rats weighing 240–260 g. The animals were divided into 5 experimental groups of 8 each. The first group of animals – intact control, the second – control pathology (without treatment); the third – animals that received the comparative drug potassium orotate at a dose of 100 mg/kg, the fourth – animals that received a dry extract of the leaves of steppe iris at a dose of 150 mg/kg and the fifth – animals that received a dry extract of the rhizomes of *Iris hungarica* at a dose 150 mg/kg.

The comparison drugs, which are analogues in terms of pharmacological action, were chosen: potassium orotate tablets (PJSC SIC "Borshchahivskiy CPP", Kyiv, Ukraine), which belongs to the group of non-steroidal anabolic agents.

*Experimental model of cardiomyopathy.*

The model of doxorubicin cardiomyopathy was reproduced by intraperitoneal injection of a solution of doxorubicin hydrochloride at a dose of 1 mg/kg, at the rate of 0.5 ml per 100 g of the animal's body weight. The solvent was sterile water. To reduce the lethality of animals, doxorubicin hydrochloride was administered according to the scheme 2 times a week for 6 weeks (a total of 42 days, total doxorubicin hydrochloride=12 mg/kg) [16, 17].

Potassium orotate at a dose of 100 mg/kg, dry extracts of steppe iris leaves and rhizomes at a dose of 150 mg/kg were administered intragastrically for 15 days, starting from the 28th day until the end of the experiment.

2 hours after the last administration of potassium orotate, dry extracts of leaves and rhizomes of steppe iris and reproduction of cardiopathology in animals under light chloroform anesthesia, an electrocardiogram was taken and removed from the experiment.

*Cardiotoxic effect and protective properties* of the studied objects were evaluated by animal survival, determination of the relative heart mass ratio, functional state of the myocardium (ECG indicators) and biochemical indicators in blood serum and heart homogenate [14, 17].

*Functional state of the myocardium (ECG indicators).*

The recording was performed at a speed of movement of the chart tape of 50 mm/s in the II lead. When deciphering the ECG, the following indicators were considered: RR – duration of a complete cardiac cycle; the duration of the PQ interval, which characterizes the time of propagation of excitation through the atria; the duration of the ventricular QRS complex and the electrical systole of the ventricles – the Q-T interval; the voltage of P, T and R waves.

The following indicators were calculated: heart rate, bpm, as the ratio of time (60 s) to the duration of the RR cardiac cycle and systolic index (SI), as the ratio of the duration of the QT interval to the duration of the RR cardiac cycle (QT/RR, %) [18].

*The level of biochemical indicators* as determined in the blood serum of animals and myocardial tissue [19, 20]:

The activity of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) using Lachem diagnostic kits (Czech Republic) [21].

The level of products of nitrogenous metabolism of urea and pyruvate using the diagnostic kit Filisit-Diagnostika (Ukraine) [22].

The intensity of LPO processes in myocardial tissue and blood serum was determined by the content of thiobarbituric acid (TBA-RP) according to the method of I. D. Stalna and T. G. Garishvili [22], reduced glutathione [23], pyruvate, and catalase activity [24].

Rats were euthanized by cutting the carotid artery under light chloroform anaesthesia [14].

Statistical analysis of the results was carried out using the standard package of the STATISTICA 6.0 program. The methods of variational statistics using parametric (one-factor analysis of variance ANOVA, Newman-Keuls test) and non-parametric methods of analysis (Kruskal-Wallis and Mann-Whitney test) were applied. The accepted level of significance is $p<0.05$ [25, 26].

**4. Research results**

To choose the optimal solvent for obtaining dry plant extracts for pharmacological research, the content of extractive substances in the leaves and rhizomes of steppe iris obtained by the method of extraction with different solvents (ethanol of different concentrations and water) was previously studied. According to the results (Table 1), it was established that ethanol (70 % v/v) and purified water extract the largest number of substances: for rhizomes, the dry residue after extraction with 70 % ethanol was 10.34±0.09 %, and for leaves – 8.21±0.15 %, respectively; water allowed to extract 10.31±0.13 % and 7.46±0.07 % of substances for rhizomes and leaves, respectively. Considering that water is a more ecological and affordable solvent, in addition, it extracts water-soluble substances (amino acids, glycosides of flavonoids, hydroxycinnamic acids, etc.) with a cardioprotective effect [27], this solvent was chosen for obtaining dry extracts from plant raw materials.

Table 1

Study of extractive substances of steppe iris leaves and rhizomes, $n$=3, $\left(\overline{x} \pm S\overline{x}\right)$

| Solvent | Dry residue, % | |
|---|---|---|
| | Rhizomes | Leaves |
| Purified water | 10.31±0.13 % | 7.46±0.07 % |
| Ethanol (30 % v/v) | 7.46±0.10 % | 6.39±0.19 % |
| Ethanol (50 % v/v) | 8.02±0.16 % | 7.43±0.12 % |
| Ethanol (70 % v/v) | 10.34±0.09 % | 8.21±0.15 % |
| Ethanol (96 %) | 3.03±0.11 % | 5.58±0.08 % |

The study of the chemical composition of the obtained aqueous extracts of leaves and rhizomes of steppe iris was carried out by the HPLC method using standard samples of phenolic compounds (Table 2).

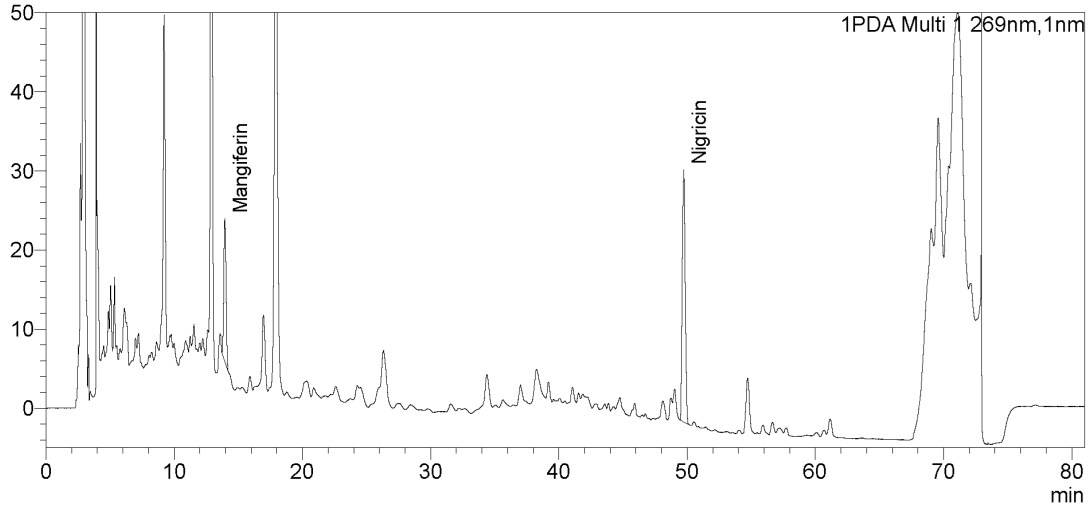
Table 2

Results of determination of phenolic compounds in dry aqueous extracts of leaves and rhizomes of steppe iris, mg/g, $n$=3, $\left(\overline{x} \pm S\overline{x}\right)$ by the HPLC method

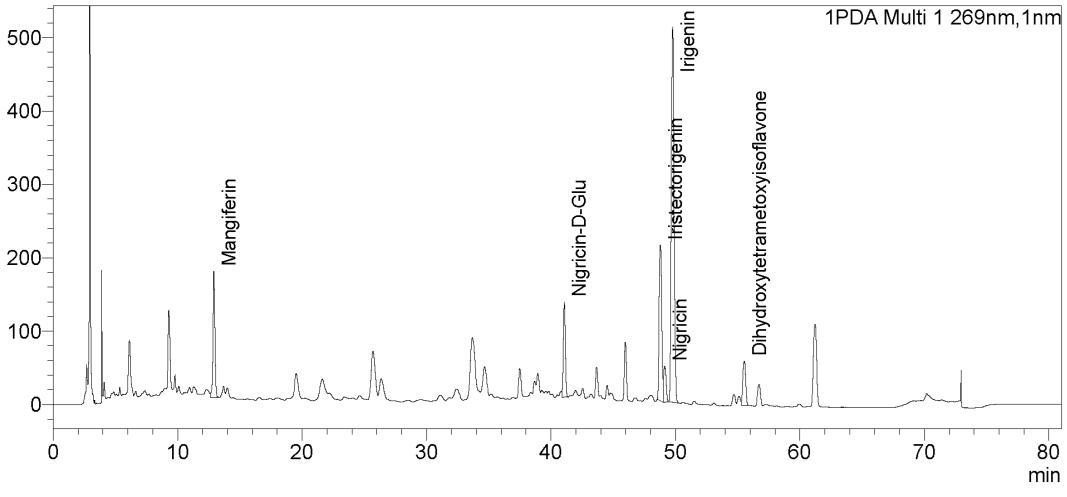
| No. | Compound name | RT, min | Rhizomes extract | Leaves extract |
|---|---|---|---|---|
| 1 | Chlorogenic acid | 9.78 | 0.78±0.07 | – |
| 2 | Mangiferin | 12.92 | 0.63±0.09 | 1.71±0.11 |
| 3 | Isoorientin | 16.74 | – | 0.52±0.12 |
| 4 | Astragalin | 18.32 | 0.79±0.16 | – |
| 5 | Ferulic acid | 22.60 | – | 0.15±0.03 |
| 6 | Nigricin-4′-O-β-D-glucoside | 41.09 | 0.85±0.11 | – |
| 7 | Cinnamic acid | 44.53 | 0.27±0.02 | – |
| 8 | Genistein-7-O-β-D-glucoside | 46.71 | 2.43±0.13 | 0.08±0.002 |
| 9 | Iristectorigenin B | 48.82 | 0.28±0.10 | – |
| 10 | Nigricin | 49.15 | 0.64±0.08 | 0.45±0.11 |
| 11 | Irigenin | 49.79 | 3.97±0.07 | – |
| 12 | 5,6-Dihydroxy-7,8,3′,5′-tetramethoxyisoflavone | 55.54 | 0.11±0.09 | – |
| Total content of identified substances | | | 10.75±0.52 | 2.91±0.12 |

In the dry water extract of steppe iris rhizomes, the content of phenolic compounds is significantly higher (10.75 mg/g) than in the extract of iris leaves (2.91 mg/g). However, the dry extract of steppe iris leaves has a slightly higher mangiferin content and, in addition, contains isorientin and ferulic acid. The rhizome extract mainly contains isoflavonoids, among them ginstein-7-glucoside (2.43 mg/g) and irigenin (3.97 mg/g), nigricin (0.64 mg/g) are dominant, and in addition, the presence of the flavonoid astragalin (0.79 mg/g), which exhibits a cardioprotective effect due to its antioxidant, antiapoptotic and anti-inflammatory activity [28].

Previous studies [29] of the dry aqueous extract of steppe iris rhizomes additionally showed the presence of pyroglutamic acid (1.34 mg/g), which also indicates the promising nature of the selected raw material for the development of drugs with cardioprotective action (Fig. 2) [30].




*a*




*b*

Fig. 2. Typical HPLC chromatograms of dry aqueous extracts of steppe iris leaves (*a*) and rhizomes (*b*) at a wavelength of 269 nm

The severity of the course of experimental cardiomyopathy was affected by the general condition of rats with control pathology who did not receive treatment. The development of myocardial pathology (Table 3) was accompanied by heart rhythm disturbances (HR decrease by 19 %), a significant expansion of the ventricular potential (*QRS* increases by 50 %), numerically increased ventricular polarization (*R*) and ventricular repolarization (*T*) potential by 20 % and 36 % in relation to the group of intact control rats, respectively; excitation of the ventricles at the time of systole (the *QT* interval increased by 43 %).

The development of ischemia is indicated by the displacement of the *ST* segment from the isoline by 62 % compared to the group of intact control animals. A probable increase in the mass ratio of the heart (Table 3) indicates the development of exudative and proliferative processes in the myocardium, which confirms the severity of the pathology.

In the group of animals that were treated with dry extract of steppe iris leaves, animal survival decreased by 87 %. At that time, in other experimental groups, the animal survival rate corresponded to 100 % (Table 3).

The therapeutic use of dry extracts of leaves and rhizomes of steppe iris, the comparison drug potassium orotate in the condition of the development of doxorubicin cardiomyopathy (Table 4), demonstrated an effect on the parameters of electrocardiography of the heart.

As the results of the study showed, the comparative drug potassium orotate under the condition of doxrubicin cardiomyopathy showed an effect on some ECG parameters: a numerical increase in heart rate (+4 %), a decrease in the time of propagation of the *QRS* potential of the ventricles by 17 % ($p<0.05$), excitation of the ventricles at the moment systole decreased by 22 % (*QT* interval) and ventricular repolarization potential by 12 % ($p<0.05$), *ST* segment decreased by 38 % ($p<0.05$) in relation to control pathology (Table 4). The relative weight ratio of the heart approached the intact control (Table 3).

In the group of animals that received the dry aqueous extract of steppe iris rhizomes at a dose of 150 mg/kg, there was a slight numerical increase in heart rate (+7 %), a decrease in the time of propagation of the *QRS* potential of the ventricles by 17 % ($p<0.05$), excitation of the ventricles in the moment of systole decreased by 22 % (*QT* interval), the repolarization potential of *T* ventricles decreased by 37 % ($p<0.05$) and the *ST* segment decreased by 26 % ($p<0.05$) in relation to control pathology (Table 4). The relative weight ratio of the heart approached the intact control (Table 3).

Against the background of administration to animals of a dry extract of steppe iris leaves at a dose of 150 mg/kg, the heart rate almost did not change (+1 %), but the time of propagation of the ventricular *QRS* potential decreased by 17 % ($p<0.05$), the excitation of the ventricles at the time of systole decreased by 18 % (*QT* interval), the repolarization potential of *T* ventricles by 12 % and the *ST* segment by 21 % ($p<0.05$) in relation to animals with control pathology (Table 4). The relative ratio of heart mass approached the control pathology (Table 3).

Therefore, the analysis of indicators of the functional state of the conducting system of the heart shows that the 15-day use in the treatment of animals with doxorubicin cardiomyopathy of the dry extract of the leaves and rhizomes of steppe iris at a dose of 150 mg/kg demonstrates a cardioprotective effect at the initial stage.

It was established that the dry extract of steppe iris rhizomes at a dose of 150 mg/kg prevailed over the dry extract of steppe iris leaves at a dose of 150 mg/kg in the numerical expressiveness of the following ECG indicators – heart rate, *QT* interval, repolarization potential of *T* ventricles and *ST* segment, and the comparison drug – potassium orotate in a dose of 100 mg/kg according to the expressiveness of the following ECG indicators – heart rate, *QT* interval, ventricular repolarization potential *T*.

The results of the studied biochemical parameters indicate the toxic effect of doxorubicin on the myocardium of rats [25], which was manifested by changes in blood serum and heart homogenate. Thus, in the blood serum of rats with control pathology, the activity of marker enzymes ALT, AST, the intensity of pyruvate, and the level of uric acid increased; and in the heart homogenate, the intensity of reduced glutathione, catalase activity, and pyruvate level decreased, and the intensity of TBA-active substances increased compared to the intact control (Table 5).

In the group of animals treated with the comparative drug potassium orotate at a dose of 100 mg/kg, dry extracts of steppe iris leaves and rhizomes at a dose of 150 mg/kg, there was a probable decrease in the activity of ALT, AST, the level of uric acid and an increase in the level of pyruvate in the blood serum; and in the heart homogenate, the intensity of reduced glutathione, catalase activity increased, and the intensity of TBA-active substances and the level of pyruvate decreased in comparison with the control pathology.

In the blood serum of animals, under the influence of the dry extract of the rhizomes of steppe iris, a 1.2-fold decrease in ALT can be observed, compared to the control pathology and almost corresponding to the indicators in the groups of animals treated with potassium orotate and dry extract of the leaves of steppe iris.

Table 3

Effect of dry extracts of leaves and rhizomes of *Iris hungarica* on lethality and heart mass ratio of rats in the doxorubicin model of cardiomyopathy, $\left(\overline{x} \pm S\overline{x}\right)$, $n$=5

| Indicator | Conditions of the experiment | | | | |
|---|---|---|---|---|---|
| | Intact control | Control pathology | Potassium orotate, 100 mg/kg | Dry extract of steppe iris leaves, 150 mg/kg | Dry extract of steppe iris rhizomes, 150 mg/kg |
| Survival rate, % | 100 | 100 | 100 | 87 | 100 |
| Mass ratio of the heart | 0.32±0.008 | 0.36±0.009* | 0.30±0.010** | 0.34±0.015^**/*** | 0.33±0.013**/*** |

*Note: * – p<0.05 – the differences are statistically significant relative to intact controls; ** – p<0.05 – the differences are statistically significant in relation to control pathology; *** – the differences are statistically significant for the potassium orotate group, ^ – 0.05<p<0.100 – the value is heading towards the reliable.*

The dry extract of the rhizomes of steppe iris reliably reduced AST in blood serum by 1.2 times ($p$<0.05), relative to the control pathology and by 1.1 times ($p$<0.05), relative to the effect of potassium orotate and approaching the level of intact control

The level of urea in the blood serum probably decreased with the use of the dry extract of steppe iris rhizomes by 1.4 times ($p$<0.05), compared to the control pathology and by 1.1 times ($p$<0.05), compared to the action of potassium orotate and in 1.2 times, relative to the dry extract of steppe iris leaves.

The dry extract of the rhizomes of steppe iris reliably increased the level of pyruvate in the blood serum of animals by 1.5 times ($p$<0.05), relative to the control pathology, and by 1.6 times ($p$<0.05) less, relative to the action of potassium orotate and approximation to the rate of intact control.

In the heart homogenate, potassium orotate, dry extracts of steppe iris rhizomes and leaves significantly increased the intensity of reduced glutathione by 1.8 times ($p$<0.05), 1.5 times ($p$<0.05) and 1.6 times ($p$<0.05), relative to control pathology; and experimental extracts were slightly inferior to the comparison drug - potassium orotate.

The intensity of TBA-active substances in the heart homogenate probably decreased as follows: the dry extract of steppe iris leaves showed the most pronounced effect by 2.4 times, under the action of the dry extract of steppe iris rhizomes by 1.7 times ($p$<0.05), and under by the action of potassium orotate – 1.6 times ($p$<0.05), compared to the control pathology.

Catalase activity in the heart homogenate was significantly increased in the groups of animals treated with the dry extract of steppe iris rhizomes by 1.4 times ($p$<0.05) and the dry extract of steppe iris leaves by 1.5 times ($p$<0.05), relative to the control pathology and prevailed over the comparison drug potassium orotate by 1.2 times and 1.1 times ($p$<0.05), respectively.

Table 4

The effect of dry extracts of steppe iris leaves and rhizomes on the functional state of the myocardium in rats based on the model of doxorubicin cardiomyopathy, $(\bar{x} \pm S\bar{x})$, $n$=5

| Conditions of the experiment | Indicators | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *HR*, beats/min | *SI*, % | *PQ*, s | *QRS*, s | *QT*, s | *R*, mV | *P*, mV | *T*, mV | *ST*, mV | *S*, mV |
| Intact control | 481±10 | 46±1.4 | 0.042± ±0.003 | 0.014± ±0.001 | 0.058± ±0.001 | 0.56± ±0.041 | 0.10± ±0.007 | 0.14± ±0.013 | 0.013± ±0.001 | 0.16± ±0.024 |
| Control pathology | 403±15* | 56±3.3* | 0.047± ±0.002 | 0.021± ±0.001* | 0.083± ±0.004* | 0.67± ±0.081 | 0.10± ±0.013 | 0.19± ±0.01* | 0.034± ±0.005* | 0.20± ±0.076 |
| Potassium orotate, 100 mg/kg | 420±10* | 45±0.8** | 0.050± ±0.001* | 0.018± ±0.001*/** | 0.065± ±0.002#^ | 0.65± ±0.043 | 0.12± ±0.007 | 0.17± ±0.013^ | 0.021± ±0.003*/** | 0.16± ±0.033 |
| Dry extract of steppe iris leaves, 150 mg/kg | 408±13* | 46±3.6** | 0.049± ±0.003 | 0.018± ±0.001*/** | 0.068± ±0.005*/** | 0.58± ±0.048 | 0.13± ±0.016 | 0.17± ±0.021º | 0.019± ±0.001** | 0.25± ±0.065 |
| Dry extract of steppe iris rhizomes, 150 mg/kg | 430±8* | 46±1.3** | 0.047± ±0.002 | 0.018± ±0.001*/** | 0.065± ±0.002 #^ | 0.68± ±0.099 | 0.10± ±0.012 | 0.12± ±0.026** | 0.025± ±0.003*/** | 0.17± ±0.021 |

*Note: * – p<0.05 – the differences are statistically significant relative to intact controls; ** – p<0.05 – the differences are statistically significant in relation to control pathology; # – 0,05<p<0.100 – the differences are statistically significant relative to intact controls; ^ – 0.05<p<0.100 – the differences are statistically significant in relation to control pathology; º – 0,05<p<0.100 – the differences are statistically significant for potassium orotate*

Table 5

Effect of dry extracts of leaves and rhizomes of steppe iris on biochemical indicators in blood serum and heart homogenate in the model of doxorubicin cardiomyopathy, $(\bar{x} \pm S\bar{x})$, $n$=5

| Indicators | Conditions of the experiment | | | | |
|---|---|---|---|---|---|
| | Intact control | Control pathology | Potassium orotate, 100 mg/kg | Dry extract of steppe iris leaves, 150 mg/kg | Dry extract of steppe iris rhizomes, 150 mg/kg |
| In blood serum | | | | | |
| AlAT, μkat/l | 0.43±0.07 | 0.39±0.03 | 0.30±0.01*/** | 0.35±0.02****$^T$ | 0.33±0.03 |
| AsAT, mqat/l | 0.57±0.02 | 0.67±0.01* | 0.63±0.01*/** | 0.59±0.02** | 0.55±0.02**/*** |
| Urea, mmol/l | 4.53±0.21 | 8.38±0.49* | 5.47±0.44*$^T$/** | 5.78±0.39*/** | 4.96±0.26** |
| PVA, mmol/g | 0.042±0.003 | 0.026±0.003* | 0.062±0.012** | 0.035±0.002**/*** | 0.039±0.001**/*** |
| In heart homogenate | | | | | |
| FH, μmol/g | 5.72±0.09 | 2.96±0.17* | 5.31±0.13*/** | 4.88±0.17*/** | 4.56±0.09*/**/*** |
| TBA-active substances, μmol/g | 38.67±2.30 | 72.01±3.95* | 44.32±2.67** | 30.55±2.95**/*** | 42.88±9.43** |
| Catalase, μmol/(min*h) | 20.44±3.62 | 12.22±1.73* | 14.09±1.30 | 18.58±1.38**/***$^T$ | 17.01±1.37** |
| PVA, mmol/g | 0.129±0.011 | 0.023±0.005* | 0.072±0.001*/** | 0.068±0.002*/**/*** | 0.098±0.012*/** |

The dry extract of the rhizomes of steppe iris showed a pronounced effect on the probable increase in the level of pyruvate in the heart homogenate by 0.075 times ($p<0.05$), than potassium orotate – by 0.049 times ($p<0.05$) and the dry extract of the leaves of steppe iris – in 0.045 times ($p<0.05$), relative to the control pathology, and potassium orotate prevailed by 1.5 times, respectively.

In the model of doxorubicin cardiomyopathy, dry extracts of leaves and rhizomes of steppe iris at a dose of 150 mg/kg showed a normalizing effect on biochemical indicators in blood serum and in heart homogenate and were not inferior to the action of the comparator potassium orotate at a dose of 100 mg/kg. The dry extract of steppe iris rhizomes showed the most pronounced effect on metabolism in cardiomyocytes.

**5. Discussion of research results**

Cardiomyopathy is one of the least studied conditions in modern cardiology, which is associated with difficulties in diagnosis, difficulties in selecting adequate therapy, and the lack of unambiguous criteria for assessing the severity of the disease course [31, 32]. One of the ways to determine and study methods of prevention and treatment of functional and biochemical disorders of the myocardium in this pathology is an experimental model of cardiomyopathy caused by the administration of doxorubicin hydrochloride to rats [12, 18, 33].

On the model of doxorubicin cardiomyopathy, an infusion of dry extracts of leaves and rhizomes of steppe iris at a dose of 150 mg/g, a comparison drug of potassium orotate at a dose of 100 mg/kg was established on heart electrocardiography indicators; biochemical indicators in blood serum and heart homogenate.

The use in the treatment of experimental extracts – dry extracts of leaves and rhizomes of steppe iris for 15 days shows a cardioprotective effect, which was determined at the beginning of the study, in terms of improving the functional state of the conduction system of the heart.

The dry extract of the rhizomes of steppe iris prevailed over the dry extract of the leaves of the steppe iris in the numerical expression of the following ECG indicators – heart rate by 6 %, *QT* interval – by 4 %, repolarization potential of *T* ventricles – by 25 % and *ST* segment – by 14 %; and the comparison drug – potassium orotate, according to the expressiveness of such ECG parameters – heart rate – by 3 %, the repolarization potential of the *T* ventricles – by 25 %, and according to *ST* parameters – it was lower by 12 %. In the groups of animals treated with the dry extract of steppe iris rhizomes, as well as with potassium orotate, the relative index of heart weight approached the values of the intact control.

Dry extract of steppe iris rhizomes in blood serum decreased the activity of marker enzymes ALT, AST, urea level and increased pyruvate level, and in heart homogenate – increased the intensity of reduced glutathione, catalase activity, pyruvate level and decreased the intensity of TBA-active substances.

It was established that the dry extract of steppe iris rhizomes showed a more pronounced effect on biochemical parameters in blood serum and heart homogenate than the dry extract of steppe iris leaves due to the high content of isoflavonoids in its composition (nigricin-4-O-β-D- glucoside, iristectorigenin B, nigricin, irigenin, 5,6-dihydroxy-7,8,3,5-tetramethoxyisoflavone), hydroxycinnamic acids (chlorogenic and cinnamic acids), mangiferin, astragalin.

Previous studies have established the presence of anabolic, anti-inflammatory, antioxidant and other activities in the dry extract of steppe iris rhizomes [34–36]. Therefore, it can be assumed that cardioprotective activity is defined as cardioprotective – such as anabolic and antioxidant – those that accelerate the recovery of the heart muscle, protect the heart muscle from the action of free radicals, preventing premature ageing and wear.

**Practical significance.** The dry extract of the rhizomes of steppe iris is a herbal anabolic agent for the creation of a new drug with cardioprotective and antioxidant properties for the treatment of CVD, prevention of the risk of developing complications and increasing the duration and quality of life of patients.

**Study limitations.** In the conditions of the study, there was a limitation associated with the individual non-tolerance (species sensitivity) of certain doses of doxorubicin hydrochloride by experimental animals during the simulation of doxorubicin cardiomyopathy to study the cardioprotective properties of dry extracts of leaves and rhizomes of steppe iris.

**Prospects for further research.** Cardiomyopathies are quite common - pathology of the myocardium, in which its structural or functional disorders occur, and which are not caused by coronary heart disease, hypertension, valvular defects and congenital heart diseases. Therefore, a further study is on the effect of extracts from the leaves and rhizomes of steppe iris on the morphological state of the myocardium of the left ventricle of the heart of rats with doxorubicin cardiomyopathy.

**6. Conclusions**

1. In the model of doxorubicin cardiomyopathy in rats, indicators of the functional state of the conducting system of the heart of animals after the use in the treatment of animals of dry aqueous extracts of leaves and rhizomes of steppe iris at a dose of 150 mg/kg demonstrated a cardioprotective effect at the initial stage.

2. It was established that the dry extract of the rhizomes of steppe iris prevailed over the comparison drug – potassium orotate in terms of the expressiveness of the following ECG indicators – heart rate, *T* ventricular repolarization potential, and the dry extract of steppe iris leaves – in terms of heart rate, *QT* interval, *T* ventricular repolarization potential and *ST* segment and approached the intact control relative heart weight values, as did potassium orotate.

3. Dry extract of steppe iris rhizomes in blood serum reduced the activity of marker enzymes ALT, AST, urea level and increased pyruvate level, and in heart ho-

mogenate – increased the intensity of reduced glutathione, catalase activity, pyruvate level and decreased the intensity of TBA–active substances.

4. The analysis of extractive substances showed that extraction with purified water extracted the most biologically active substances from the leaves and rhizomes of steppe iris, and this solvent was chosen to obtain dry extracts from raw materials.

5. The chemical profile of the obtained dry aqueous extracts of steppe iris leaves and rhizomes was investigated by HPLC. As a result, 12 compounds were identified: chlorogenic acid, cinnamic acid, ferulic acid, mangiferin, isoorientin, astragalin, nigricin-4′-O-β-D-glucoside, genistin-7-O-β-D-glucoside, iristectorigenin B, nigricin, irigenin, 5,6-dihydroxy-7,8,3′,5′-tetramethoxyisoflavone. Among them, genistin-7-O-β-D-glucoside, irigenin and mangiferin are dominant.

6. The obtained results indicate the ability of the dry extract of steppe iris rhizomes to correct biochemical indicators in blood serum, reducing the activity of marker enzymes ALT, AST, the level of urea and increasing the level of pyruvate, and in the homogenate of the heart – increasing the intensity of reduced glutathione, activity of catalase, the level of pyruvate and reducing the intensity of TBA-active substances, due to the high content of isoflavonoids and amino acids.

7. The dry extract of steppe iris rhizomes is a promising herbal remedy for the creation of a new drug with cardioprotective properties.

**Conflict of interest**

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study, and its results presented in this article.

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**Data availability**

Data will be provided upon reasonable request.

**Use of artificial intelligence**

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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