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STUDY OF THE CARDIOPROTECTIVE EFFECT OF HAWTHORN EXTRACT IN DOXORUBICIN CARDIOMYOPATHY

Margarita Georgievna Tuaeva[1], Saida Rizvanovna Giulmetova[2], Azaliya Ramovna Serochenkova[3], Kirill Igorevich Kovalev[3*], Ganimat Afladdinovich Gadzhiev[4], Tatiana Anatolevna Simakova[5]

1. ***Department of Therapy, Medical Faculty of First Moscow State Medical University, named after I.M. Sechenov, Moscow, Russia.***
2. ***Department of Therapy, Medical Faculty of Astrakhan State Medical University, Astrakhan, Russia.***
3. ***Department of Therapy, Medical Faculty of Tula State Medical University, Tula, Russia.***
4. ***Department of Therapy, Pediatric Faculty of Rostov State Medical University, Rostov-on-Don, Russia.***
5. ***Department of Therapy, Medical Faculty of Saratov State Medical University, named after V. I. Razumovsky, Saratov, Russia.***

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ABSTRACT

Cardioprotectors are medicinal substances that enhance the activity and operation of the heart under both normal and pathological circumstances while thwarting the effects of various corrosive agents. In this scientific work, the cardioprotective activity of hawthorn extract is evaluated on the example of laboratory rats with artificially induced doxorubicin cardiomyopathy. Corvitin was chosen as the main substance with which the main indicators are compared. In the event of using hawthorn extract, the control of body weight and organs of the tested animals revealed minimal body weight loss as well as the closest approximation of the mass of individual organs to the normal state. The conducted ECG study showed that by many indicators, the use of hawthorn extract gave a more positive result than the use of Corvitin. A similar situation is also observed when evaluating the enzymatic parameters of blood serum and the lipid peroxidation system, and the antioxidant system. Thus, it was demonstrated through experimentation that the hawthorn extract under study prevents the development of doxorubicin myocardial intoxication in white rats and has a noticeable normalising effect on the heart muscle's functional state, not inferior in effect to Corvitin, and in some indicators, even exceeding it.

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Introduction

Prevention and treatment of cardiovascular diseases remains an urgent problem today. Chronic heart failure remains one of the most common, progressive and prognostically unfavorable diseases of the cardiovascular system. Mortality from chronic heart failure also remains high. For all cases of chronic heart failure, regardless of the cause and functional class, the annual mortality is relatively constant and is 10%; 5-year mortality is 62% among men and 43% among women [1]. Patients suffering from chronic heart failure are forced to take a large number of medications for a long time, which increases the risk of adverse reactions.

The word "cardioprotectors" refers to medicinal substances that enhance the work and operation of the heart both in healthy settings and in a variety of diseased circumstances, thereby halting the effects of numerous harmful substances [2]. An important indicator of the myocardium's function, cellular metabolism, ionic balance, and potential structural and functional alterations in cardiomyocyte membranes is cardioprotective activity [3].

Corresponding Author: Kirill Igorevich Kovalev; Department of Therapy, Medical Faculty of Tula State Medical University, Tula, Russia. E-mail: bucky99@ya.ru.

Long-term experience demonstrates that when using the antitumor drug doxorubicin, especially when its cumulative dose is exceeded by more than 450–550 mg/kg, a disease similar to dilated cardiomyopathy is observed, with the same clinical and morphological symptoms [4].
In the mechanism of the specific cardiotoxic action of doxorubicin, inhibition of the synthesis of nucleic acids and protein is separately because of its interaction with DNA and capacity to inhibit topoisomerase II, the substance was isolated [5]. The research of the pathogenesis of doxorubicin cardiomyopathy shows two more major hypotheses regarding the causes of myocardial damage. The first theory is supported by doxorubicin's increased affinity for cardiolipin, one of the most prevalent phospholipids found in cardiac muscle cells' membranes, particularly the nucleus and mitochondria [6]. The second one is based on the ability of doxorubicin to directly interfere with the oxidative metabolism of the myocardium with the acceleration of the generation of active oxygen metabolites and damage to the membranes of cardiomyocytes [7]. That is why preventive protection of the myocardium from the destructive effects of toxic compounds involves the use of drugs with a protective effect on the myocardium.
The advantage of medicines made from natural plant raw materials is low toxicity, the chances of long-term use without huge side effects [8]. In this connection, there is currently an increased interest of researchers in drugs of natural origin that have a cardiotonic effect, in particular, to medicines made on the basis of hawthorn, the cardiotonic effect of which has been known for a long time [9]. However, the major problem with the use of herbal preparations and, in particular, hawthorn preparations, is the lack of unified approaches to their standardization, which makes it difficult to adequately assess their effectiveness and safety of use in patients with chronic heart failure. Thus, different parts of a medicinal plant contain different amounts of ingredients that cause pharmacological activity. In terms of the content of hyperoside, the main component that causes the cardiotonic effect, hawthorn flowers exceed hawthorn leaves by almost three times, and hawthorn fruits by six to seven times. Despite this, a number of medicines made from dry hawthorn fruit extract are classified as cardiotonic medicines according to the clinical and pharmacological classification. Taking into account the above, a comparative study of the cardiotonic effect of hawthorn extracts made from various parts of the plant was carried out in the experiment and the effectiveness of the use of hawthorn extract standardized by the flavonoid hyperoside, the main component determining the cardiotonic effect, as part of the complex therapy of laboratory rats suffering from chronic heart failure was studied.

Materials and Methods

Doxorubicin cardiomyopathy was caused in non-linear white rats by twice intravenous (into the tail vein) injection of doxorubicin at a dose of 7 mg /kg with an interval of 3 days. 48 nonlinear white rats were used in the experiment. Cardiomyopathy developed on the 4th day. The studied preparation of an aqueous extract of hawthorn leaves and flowers was administered at a dose of 1.8 ml/kg intragastrically for 7 days after administration of doxorubicin [10].
A group of intact control animals took an equal volume of H2O, that was injected intragastrically using a cannula. On the 6th day of the experiment, the percentage of survival was taken into account in groups of animals; an electrocardiogram was recorded, for which the rats were anesthetized by intraperitoneal administration of 1% barbamil solution at a dose of 0.8 ml / 100 mg of body weight.
Corvitin was chosen as a comparison drug. The reference drug was administered intragastrically at a dose of 5 mg/kg. One of the most potent antioxidants is corvitin. It recognizes a membrane-stabilizing effect and guards against a change in the body's oxidative equilibrium [11].
After euthanasia, the activity of aspartate aminotransferase (AsAT) and creatine phosphokinase (CPK) was measured using diagnostic test kits to look for metabolic and dystrophic abnormalities in cardiac tissue "Lachema." The activity of alanine aminotransferase (AlAT) in blood serum, as an indicator of cardiomyocyte cytolysis, was analyzed by the Reitman method [12] using test kits from Lachema (Czech Republic).
Based on biochemical analysis of blood and cardiac homogenate, the amount of peroxide catabolic transformations of structural lipids in the body of white rats with doxorubicin cardiomyopathy was evaluated. The contents of diene conjugates reduced glutathione, and malondialdehyde was determined in blood and heart tissue [13].
Utilising techniques from variational statistics, the outcomes of the research conducted were statistically processed. Using Statistica, a specialised programme, calculations were performed.

Results and Discussion

Data on changes in body weight and internal organs are given in **Table 1**.
The study showed that after the administration of doxorubicin on the 6th day of the experiment, 2 animals died in a group of animals with a control pathology (doxorubicin cardiomyopathy without treatment). Therapeutic and prophylactic administration of hawthorn extract to research rats at a dose of 1.8 ml/kg primarily increased the survival of rats to 87.5%, while the use of Corvitin didn’t inhibit the increased rate of death of animals in the research group (25%, as in the group of untreated doxorubicin cardiomyopathy). The dystrophic changes provoked by the use of doxorubicin were accompanied by a significant decrease in the body weight of untreated rats as compared to the input data **(Table 1)**. Simultaneously, the rats that received hawthorn extract lost less weight, and the body weight of the rats that received the reference drug reduced thesame to with modifications seen in the group of untreated animals.

Table 1. The effect of hawthorn water extract on the body weight and internal organs of rats under conditions of doxorubicin cardiomyopathy (M=m), n=12.

Experimental conditions	Weight loss of rats, g	Mass of internal organs, g			
		Liver	Heart	Kidneys	Spleen
Intact control	+ 8.3±0.3	7.20±0.22	0.60±0.02	1.41±0.05	0.60±0.03
Untreated doxorubicin cardiomyopathy	-56.5±2.4	6.82±0.39	0.70±0.03	1.50±0.09	0.19±0.02
Doxorubicin cardiomyopathy, treatment with hawthorn extract	-38.7±1.9	7.06±0.25	0.62±0.01	1.34±0.04	0.28±0.03
Doxorubicin cardiomyopathy, treated with Corvitin	-53.6±2.6	6.91±0.34	0.66±0.01	1.59±0.06	0.18±0.014

Damage to the membrane apparatus of cardiomyocytes as a result to violations of cellular metabolism, DNA structure, and the onset of pro-oxidant pathways when doxorubicin was present disrupted the myocardium's ability to contract, which was observed during an ECG examination **(Table 2)**.

Table 2. The effect of hawthorn extract on the ECG parameters of rats against the background of doxorubicin damage to the heart muscle

Indicator	Experimental conditions			
	Intact control	Untreated doxorubicin cardiomyopathy	Doxorubicin cardiomyopathy, treatment with hawthorn extract	Doxorubicin cardiomyopathy, treated with corvitin
Heart rate, beats/min	420.1±24.6	276±10.5	398.3±14.9	300.7±23.7
PQ, c	0.040±0.002	0.053±0.004	0.043±0.002	0.048±0.004
QRS, c	0.020±0.002	0.014±0.004	0.016±0.002	0.018±0.002
Q-T, c	0.062±0.004	0.086±0.009	0.064±0.006	0.076±0.004
R, мВ	0.66±0.07	0.45±0.05	0.64±0.06	0.49±0.05
P, мВ	0.10±0.02	0.15±0.02	0.10±0.02	0.10±0.02
T, мВ	0.15±0.01	0.21±0.02	0.15±0.02	0.18±0.04
Offset ST from the isoline, mm	0	2.0±0.6	0.4±0.1	0.6±0.2

Cardiotoxicity of doxorubicin in rats of the control pathology group turned out to be a decrease in heart rate compared with the same indicator of intact control, i.e., it had the character of bradyarrhythmia.

A potential lengthening of the PQ interval, an increase in the amplitude of the T and P waves, an extension of the ventricular complex's (Q-T) duration, a potential shortening of the ST segment, and a low-amplitude QRS complex (low R wave) were also signs that the heart muscle's functional capacity was being depleted **(Table 2)**.

It was discovered for the chosen model that the investigated hawthorn extract generated certain alterations in the heart's functional activity, which was captured using an ECG. Employment of hawthorn extract in the therapeutic and prophylactic regime was expressed in the normalization of the heart rate index, the value of which almost reached the boundaries of intact animals. The amplitudes of the P and T teeth decreased significantly compared to the control pathology, and the duration of the PQ interval decreased **(Table 2)**. Noticeably, although not reliably, ECG indicators that characterize the functional state of the ventricular apparatus of the heart - the QRS complex and the Q-T interval, the amplitude of the R wave were restored.

The bradyarrhythmic nature of the heart rate was documented during the ECG test of rats that received Corvitin, almost as in untreated animals and with a large divergence from the value in intact animals **(Table 2)**. Other ECG indicators were directed to the values of intact control with an unreliable deviation from the values for the control pathology.

An increase in creatine phosphokinase activity and hyperfermentemia of AsAT in the blood serum of rats, which is observed in animals from the control pathology group, are indicators that the oxidative metabolism in the myocardium has been reoriented to anaerobic pathways as a result of doxorubicin intoxication and damage to the heart muscle **(Table 3)**.

The use of hawthorn extract helps to maintain the activity of creatine phosphokinase and lactate dehydrogenase almost at the level of intact control. The reference drug also helps to reduce the activity of AsAT and creatine phosphokinase, although the effect of hawthorn extract on these indicators is more pronounced.

Table 3. The effect of hawthorn extract on the fermentative parameters of rat blood serum on a model of doxorubicin cardiomyopathy

Experimental conditions	Enzyme activity		
	Creatine Kinase, µcat/l	**LDH, µmol/l**	**AsAT, µmol/l**
Intact control	0.42± 0.03	7.1±0.6	0.64±0.034
Untreated doxorubicin cardiomyopathy	0.92±0.09	11.2±1.2	1.36±0.026
Doxorubicin cardiomyopathy, treatment with hawthorn extract	0.54±0.04	7.4±0.4	0.96±0.03
Doxorubicin cardiomyopathy, treated with Corvitin	0.61±0.05	8.3±0.5	1.12±0.027

A large rise in the level of diene conjugate and malondialdehyde in both blood serum and myocardial homogenate is indicative of the intensification of free radical transformation of cardiomyocyte membrane lipids under the conditions of the model disease **(Table 4)**. The increased production of diene conjugate and malondialdehyde in both the cardiac homogenate and blood serum of untreated rats is indicative of the intensification of the free radical transformation of the membrane lipids of cardiomyocytes. Against the background of the use of hawthorn extract, a decrease in the level of diene conjugate reduced glutathione, and malondialdehyde was recorded in the homogenate of the heart muscle and the blood serum.
Indicators of the antioxidant system showed that reduced glutathione concentration in the blood increased, however the content of reduced glutathione in the cardiac homogenate dramatically decreased in contrast to results from undamaged animals. This reflects the depletion of glutathione protection at the organ level. Under the action of hawthorn extract, the content of reduced glutathione in the control pathology significantly reached values in the intact group: in the blood, and the myocardial homogenate, while the activity of hawthorn extract was at the level of the reference drug.

Table 4. The effect of hawthorn extract on the state of the lipid peroxidation system and the antioxidant system in doxorubicin cardiomyopathy

Indicator	Intact control	Untreated doxorubicin cardiomyopathy	Doxorubicin cardiomyopathy, treatment with hawthorn extract	Doxorubicin cardiomyopathy, treated with corvitin
	Blood serum			
Malondialdehyde, µmol/l	2,0±0,12	5,4±0,26	3,13±0,23	4,01±0,20
Diene conjugates, µmol/l	1,4±0,01	2,0±0,02	1,8±0,01	1,9±0,02
Reduced glutathione, mg%	16,2±1,2	36,9±2,3	21,4±1,8	27,7 ±2,2
	Homogenate of the heart			
Malondialdehyde, µmol/l	34,7±1,25	160,4±4,4	130,4±4,9	120,2±7,0
Diene conjugates, µmol/l	3,4±0,5	12,3±0,74	44,4±1,7	36,1±1,62
Reduced glutathione, mg%	70,4±12,8	35,2±6,41	74,2±10,5	77,8±11,6

As noted above, the opinions of various researchers agree that hawthorn preparations have negligible toxic properties. According to the unanimous conclusion of the researchers, hawthorn preparations can be taken for months or even several years, since there is no accumulation. However, in recent years it has been established that prolonged and uncontrolled intake of hawthorn or medicines developed on its basis can cause heart rate depression, therefore treatment with hawthorn must be carried out under the supervision of a doctor. Taking hawthorn fruits on an empty stomach often causes intestinal spasm, which should be taken into account when preparing a course of treatment using hawthorn extract

Conclusion

Thus, it was experimentally established that hawthorn extract hinders the development of doxorubicin myocardial intoxication in white rats, exerting a pronounced regularizing effect on the practical state of the heart muscle, not inferior in effect to Corvitin, and in some indicators, even beyond it. Indicators of the antioxidant system showed that reduced glutathione concentration in the blood increased, however the content of reduced glutathione in the cardiac homogenate dramatically decreased in contrast to results from undamaged animals.
The mentioned alteration indicate the cardioprotective features of hawthorn extract. It considers how doxorubicin damages the heart and the dynamics of lipid peroxidation/antioxidant system parameter changes brought on by hawthorn extract in the context of experimental pathology. It can be assumed that the therapeutic efficiency of the studied agent for the chosen model is determined by the direct dependence of the severity of the cardioprotective effect on the strength of the antioxidant influence. It's possible that thanks to these mechanisms, the ability of hawthorn extract to stop a shift in oxidative metabolism as well as ensure the integrity and functional ability of cardiomyocytes is realized.

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Ethics statement: The protocol for experiments with laboratory animals complied with the requirements of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes.

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