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ANTI-EDEME EFFECT OF DIHYDROQUERCETIN COMPOSITION AND ARABINO GALACTAN UNDER THE CONDITIONS OF THE MODEL OF CHRONIC VENOUS INSUFFICIENCY

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The antiedematous activity of the composition of dihydroquercetin and arabinogalactan was studied in a model of chronic venous insufficiency caused by partial occlusion of the caudal vena cava. Animals of the experimental group were intragastrically injected with a composition of dihydroquercetin and arabinogalactan (50 and 250 mg/kg, respectively) once a day for two weeks. The antiedematous effect of the composition of dihydroquercetin and arabinogalactan was evaluated oncometrically and morphologically. Microcirculation in the leg tissues was measured by laser Doppler flowmetry. Venous pressure in the vena cava was recorded by the direct method on a Biopac electrophysiological apparatus. The development of edema of the hind limbs, venous hypertension, and a decrease in the level of microcirculation in the skin in rats under conditions of a model of chronic venous insufficiency were shown. It has been established that a course intragastric administration of a composition of dihydroquercetin and arabinogalactan prevents an increase in the volume of the hind limbs and interstitial space, reduces venous pressure and improves microcirculation in rats under conditions of chronic venous insufficiency.

Keywords: chronic venous insufficiency, venous pressure, edema, microcirculation, dihydroquercetin, arabinogalactan.

Despite significant advances in the pharmacotherapy of chronic diseases of the veins of the lower extremities, the problem of one of the most common symptoms, edema, still remains an important problem [1]. The most important mechanism for the development of edema in chronic venous insufficiency (CVI) is venous hypertension, which leads to impaired functioning of veins, capillaries, and lymphatic vessels [12]. Drug therapy of this symptom of CVI is aimed at improving lymphatic drainage, reducing capillary permeability, restoring microcirculation

ions, i.e. correction of fluid reabsorption from tissues [1, 11].

Currently, flavonoids (diosmin, rutin) and their derivatives (rutosides) are considered to be one of the most effective phleboprotectors [2, 13]. One of the promising phleboprotectors is the flavonoid dihydroquercetin, which

ry shows lymphokinetic and capillary protective activity [4, 6]. An experiment on the study of tissue blood flow showed that the use of dihydroquercetin in combination with arabinogalactan increases its ability to enhance microcirculation [7].

In this regard, the purpose of this work was to study the antiedematous activity of the composition of dihydroquercetin and arabinogalactan in rats with chronic venous insufficiency.

MATERIAL AND METHODS

The experiments were performed on 21 outbred male Wistar rats weighing 300–350 g, obtained from the vivarium of the E.D. Goldberg SO RAMS. The animals were kept in plastic cages under standard conditions with a 12:12 light cycle and free access to water and food. Research performed

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not in accordance with the principles of humanity set out in the Directives of the European Community (86/609/EEC) and the Declaration of Helsinki for the Protection of Vertebrate Animals used for Laboratory and Other Purposes.

CVI was modeled by restricting blood flow in the caudal vena cava for two weeks [8]. On the first day of the experiment, animals under ether anesthesia underwent laparotomy, a section of the caudal vena cava was isolated proximal to the right renal vein, and a ligature was placed under it, after which heparin was injected into the femoral vein at a dose of 250 U/kg and partial occlusion of the caudal vein was performed. vein (by 2/3) using a needle with a section diameter of 0.8 mm, which was applied to the vein at the site of ligation. After ligation of the vessel, the lumen of the vessel was partially restored by removing the needle. In sham operated (LS) animals, the surgical intervention was completely repeated, but without the stage of vessel occlusion. From the second day of the experiment until the end of the second week, the animals received the test substance daily. The composition of dihydroquercetin and arabinogalactan was administered intragastrically at a dose of 300 mg/kg (50 mg of dihydroquercetin and 250 mg of arabinogalactan) as a suspension in purified water. Animals of the control and LO groups received purified water in an equivalent volume. The last introduction of substances was carried out one hour before the measurement of parameters

On the 14th day, the foot volume of the hind limbs was assessed in animals by the oncometric method [9], venous pressure and the level of microcirculation in the superficial tissues of the lower leg were measured. The day before the measurements, the hind limbs of the animals were depilated from the inside. The level of microcirculation was assessed by laser Doppler flowmetry using a hardware complex for electrophysiological studies Biopac

(USA), BPU (blood perfusion unit) was used as a microcirculation unit. Before measuring venous pressure, rats were anesthetized with diethyl ether, then heparin was administered intravenously at a dose of 250 U/kg.

The pressure in the caudal vena cava was measured by a direct method using a TSD104A pressure sensor of the Biopac hardware complex. Access was through the femoral vein.

After euthanasia (an overdose of ether anesthesia), a part of the leg muscle was taken from the animals. For histological examination, muscle pieces were fixed in 10% neutral formalin, then dehydrated in a series of alcohols of increasing concentration, embedded in paraffin, and cross sections were made 5 μ m thick. Deparaffinized sections were stained with hematoxylin and eosin. On histological preparations of the calf muscle using the Adobe Photoshop CS2 program, we assessed the area of the interstitial space in relation to the standard tissue area (in %) in the fields of view at 10x magnification.

The significance of intergroup differences was assessed using the nonparametric Mann–Whitney test. The research results are presented as $M \pm m$, where M is the mean value, m is the standard error of the mean

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RESULTS AND DISCUSSION

Animals of the control group developed edema of the hind limbs on the 14th day, which was expressed in a significant increase in the volume of the feet by 9% compared with the initial values (Table 1). Restriction of blood flow in the caudal vena cava led to an increase in venous pressure by 2.2 times ($p < 0.05$) compared with LO animals (Table 2). Against the background of venous hypertension in the control group, a decrease in the

Table 1

Influence of a course (14 days) intragastric administration of a composition of dihydroquercetin and arabinogalactan (50 and 250 mg/kg, respectively) on the foot volume of the hind limbs in rats with chronic venous insufficiency

group of animals	Initial volume, ml		Volume on the 14th day, ml	
	Left foot	Right foot	Left foot	Right foot
LO ($n = 7$)	2.01 \pm 0.09	1.99 \pm 0.11	2.00 \pm 0.05	2.01 \pm 0.05
Control ($n = 7$)	2.06 \pm 0.04	2.06 \pm 0.04	2.24 \pm 0.05*#	2.25 \pm 0.04*#
Dihydroquercetin and arabinogalactan ($n = 7$)	2.01 \pm 0.05	2.00 \pm 0.05	2.02 \pm 0.06+	2.01 \pm 0.06+

Note. Here and in Table. 2 shows statistically significant ($p < 0.05$) differences from the values of the corresponding indicators: * - group LO, + - control, # baseline values.

table 2

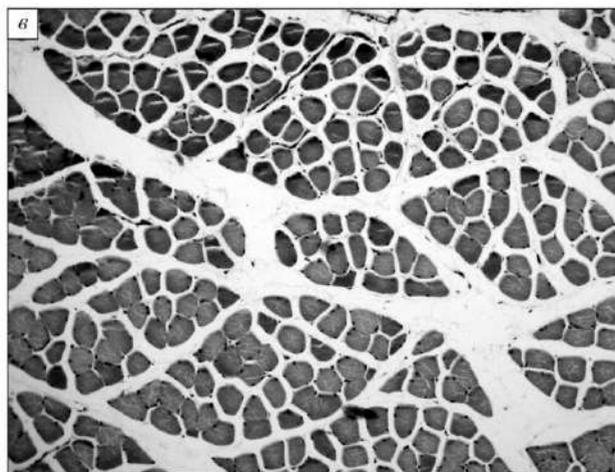
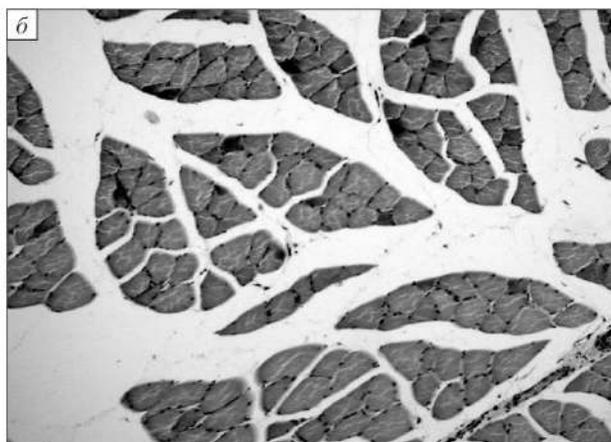
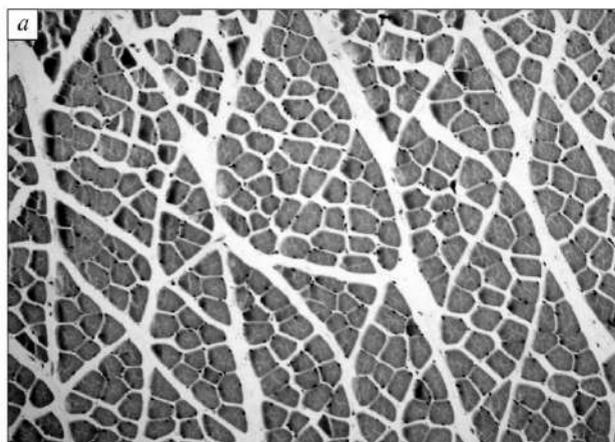
Effect of course (14 days) intragastric administration of a composition of dihydroquercetin and arabinogalactan (50 and 250 mg/kg, respectively) on venous pressure, microcirculation, and interstitial space in rats with chronic venous insufficiency

group of animals	venous pressure, mmHg Art.	BPU, rel. units	Interstitial area space in relation to the standard fabric area, %
LO ($n = 7$)	4.52 ± 0.18	743 ± 65	32.9 ± 0.9
Control ($n = 7$)	$9.74 \pm 0.33^*$	$502 \pm 19^*$	$41.1 \pm 1.5^*$
Dihydroquercetin and arabinogalactan ($n = 7$)	$8.14 \pm 0.32^* +$	$592 \pm 29^* +$	$36.5 \pm 0.6^+$

the improvement of microcirculation in the tissues of the lower leg by 32% compared with LO animals (see Table 2). Histological examination revealed an increase in the interstitial space by 25% in the control group ($p < 0.05$) (see Table 2, figure).

Thus, partial occlusion of the caudal vena cava leads to limb edema, the development of venous hypertension, and a decrease in the level of microcirculation in the skin; the model reproduces the characteristic signs of CVI in humans [8]. It is known that edema in CVI is due to

disorders of venous and lymphatic outflow at the macrohemodynamic level, which lead to disorganization of the regional microcirculation system [5]. A long-term increase in pressure in the veins of the lower extremities leads to their expansion, pathological deposition of blood, and, as a result, an increase in transcapillary filtration [3]. Over time, due to the increased volume of interstitial fluid, overload and decompensation of the lymphatic system of the lower extremities and the development of persistent edema occur [12].



Rice. Muscles of the leg of rats. Sham operated animals (a), animals with chronic venous insufficiency (b), and animals with chronic venous insufficiency treated intragastrically with a composition of dihydroquercetin and arabinogalactan (50 and 250 mg/kg, respectively) (c). Edema of the interstitial space. Staining with hematoxylin and eosin, $\times 10$

The introduction of the composition of dihydroquercetin and arabinogalactan under the conditions of the CVI model prevented the formation of limb edema (see Table 1). Thus, the volume of the foot of the hind limbs in rats treated with the composition of dihydroquercetin and arabinogalactan was significantly lower compared to the values in the control and did not differ significantly from the values in the LO animals. Venous pressure in this group was significantly lower by 16% compared to the control group (see Table 2). In addition, there was an improvement in microcirculation in the superficial tissues of the lower leg in experimental animals (see Table 2). The level of microcirculation in the group of animals treated with the composition of dihydroquercetin and arabinogalactan was significantly higher by 18% compared to the value in control animals. According to the histological examination, the studied composition significantly limited the increase in the area of the interstitial space (see Table 2, figure).

The data obtained indicate the prospects for the development of a new phlebotropic drug based on the composition of dihydroquercetin and arabinogalactan.

CONCLUSION

The composition of dihydroquercetin and arabinogalactan during course administration to rats with CVI model in our study demonstrated the ability to prevent an increase in the volume of the hind limbs and the area of the interstitial space, reduce venous pressure, and increase microcirculation in the skin.

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**ANTIEDEMATOUS EFFECT OF THE DIHYDROQUERCETIN
AND ARABINO GALACTAN COMPOSITION IN chronic venous
insufficiency model**

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Antiedematous activity of the dihydroquercetin and arabinogalactan composition in animal model of chronic venous insufficiency induced by partial occlusion of the caudal vena cava was investigated. Course (14 days) intragastric administration of composition based on dihydroquercetin and arabinogalactan (50+250 mg/kg, respectively) was given. Antiedematous effect of the dihydroquercetin and arabinogalactan composition was evaluated by oncometry and morphological methods. Microcirculation in the tissues of the leg was measured by laser Doppler flowmetry. Venous pressure in the vena cava was recorded by the direct method on the apparatus for electrophysiological studies "Biopac". Edema of lower limbs, venous hypertension and reduction in cutaneous microcirculation was found on rat's model of chronic venous insufficiency. It was established that course intragastric administration of dihydroquercetin and arabinogalactan composition prevented increase in the hindlimb's circumference and area of the interstitial space, reduced venous pressure and improved microcirculation in rats with chronic venous insufficiency.

Key words: chronic venous insufficiency, venous pressure, edema, microcirculation, dihydroquercetin, arabinogalactan.

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