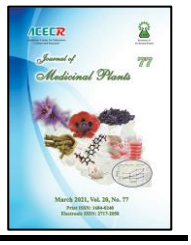
J. Med. Plants 2021; 20(77): 60-78

Institute of Medicinal Plants

Journal of Medicinal Plants

Journal homepage: www.jmp.ir



Research Article

Some aspects of the adaptogenic potential of European mistletoe (*Viscum album* L.) extracts under variable physical performance

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ARTICLE INFO

Keywords:
European mistletoe
Viscum album L.
Santalaceae
Adaptogens
Antioxidant
Energy metabolism
Stress

ABSTRACT

Background: Stress is an integral part of human life and leads to maladaptation of the organism and needs rational pharmacological correction. **Objective:** The purpose of this experiment was to evaluate the adaptogenic potential of European mistletoe extracts. **Methods:** The work was performed on Balb/c mice. The test-objects were ethanol and aqueous extracts of European mistletoe (*Viscum album* L., Santalaceae) collected from pear and black poplar in dose 100 mg/kg (P.O.). Physical overloads were modeled in the forced swimming test. The analyzed parameters were: the duration of animals swimming, changes in the parameters of mitochondrial respiration, the concentration of ATP, activity of caspase-3, and apoptosis-inducing factor in the muscles and lactic acid in the blood serum of animals. The state of the pro / antioxidant system and acute toxicity of the test-extracts was also evaluated. **Results:** The study found that the LD_{50} of the test-extracts was more than 5000 mg/kg (P.O.). Ethanol extracts (40 and 70 %) with a single administration had the greatest impact on the physical strain of mice. In the course administration of 40 % ethanol mistletoe extracts the swimming time of mice was increased by 3.4 and 5.05 times ($P < 0.05$) from black poplar and pear, respectively. Also, the use of 40 % extracts contributed to the normalization of the pro/antioxidant balance, the restoration of the cell energy metabolism, and the decrease of the intensity of the apoptotic reactions. **Conclusion:** The study showed that the 40 % ethanol extracts from European mistletoe (host plants: pear and black poplar) potentially can be used as adaptogenic agents.

1. Introduction

Currently, stress is an integral part of human life. According to the World Health Organization, about 70-90 % of the total number of visits to primary care medical specialists is associated with acute stress or with chronic diseases associated with stress [1]. Statistics show that more than 450 million people are affected by stress disorders, and by 2020 their number may increase by 15 % [2].

Abbreviations: P.O., Orally, LD_{50}, Medium Lethal Dose

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doi: 10.29252/jmp.20.77.60
Received 24 May 2020; Received in revised form 9 November 2020; Accepted 14 November 2020

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[DOI: 10.52547/jmp.20.77.60]

Stress is defined as a non-specific influence of a negative factor on the human body leading to disruption of homeostasis and maladaptation, which is counteracted by an adaptive (protective) mechanisms, including behavioral, biochemical, cognitive, and physiological reactions [3]. The main stress factors include physical (noise, light, vibration), chemical, and biological factors. The consequences of the disadaptive factor action a person is most often negative and manifest as a deterioration in physical strain and cognitive dysfunction [4]. It was established that stress underlies the deterioration of a person's physical well-being, which is expressed in the loss of physical performance [5]. As a result, people suffering from the stress factor and associated with it physical inactivity have an increased risk of obesity, diabetes mellitus, cancer, diseases of the cardiovascular system, a deterioration in the immune response, behavioral and cognitive impairment [6]. As you can see, stress is a serious medical and social problem, the treatment and prevention of which is an urgent task of modern medicine and pharmacology. Adaptogens are one of the pharmacotherapeutic groups that contribute to increasing the body's resistance to the stressor action [7]. The term adaptogens was proposed in 1940 by N. Lazarev, after studying the biological activity of *Schisandra chinensis* (Turcz.) Baill. According to the modern concept, adaptogens are defined as agents, mainly of plant origin, that have a non-specific effect and increase the body's resistance to a wide range of stressors (physical, chemical, and biological) [8]. To date, a large number of studies have been conducted on the adaptogenic activity of plant extracts and their isolates. The main directions of the study of adaptogens are focused on: 1) phytochemical analysis of plants with adaptogenic activity; 2) the study of mechanisms for the implementation of adaptogenic action at the cellular and molecular levels; 3) assessment of the pharmacological effectiveness and safety of potential adaptogenic agents in animals and humans; 4) the development of dosage forms of adaptogens that have shown a high level of effectiveness and have an optimal toxicological profile [9]. Moreover, the most promising studies are work aimed at studying the effectiveness, safety, and mechanisms of action of adaptogens [10]. This study focused on assessing certain toxicological parameters, pharmacological efficacy (effect on physical performance), and possible mechanisms of action of various extracts of European mistletoe (*Viscum album*) in mice under conditions of physical exertion. European mistletoe is an evergreen semi-parasitic shrub that grows on the branches of various larch trees (oak, apple, pear, poplar) [11]. Mistletoe contains various types of biologically active substances: polysaccharides, flavonoids, amino acids, triterpene acids, glycoproteins (lectin) [12]. The antineoplastic properties of mistletoe extracts are widely known [13]. The result of a study showed that the use of mistletoe preparations improved the quality of life in patients with metastatic pancreatic cancer [14]. The effectiveness of extracts from mistletoe with endometriosis was also studied [15]. In this case, no significant adverse reactions with the use of mistletoe preparations were recorded [16]. However, despite the evidence of the mistletoe preparations effectiveness as anticancer agents, the study of other types of pharmacological activity of extracts obtained from European mistletoe may be of undoubted scientific and practical interest.

Extracts obtained from European mistletoe are characterized by the presence of a wide range of biologically active substances, including lectins, flavonoids, phenolic acids, terpenoids, sterols, phenylpropanoids, and alkaloids. The

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rich chemical composition and potentially low toxicity make mistletoe extracts potentially effective adaptogens that can correct negative changes in muscle tissue that occur in conditions of excessive physical overload. The aim of the study was, evaluate the adaptogenic potential of European mistletoe (*Viscum album* L., Santalaceae) extracts in experimental physical performance.

2. Materials and Methods

2.1. Animals

The study was performed on 310 Balb/c male mice weighing 25 - 27 grams. Animals were obtained from the vivarium of the Pyatigorsk Medical and Pharmaceutical Institute. For the experiment duration mice were placed in T-2 macrolon boxes with free access to water and food. Laid material - wood granular fraction was changed 1 time in 3 days. Ambient temperature 22 ± 2 ºC, relative humidity 60 ± 5 %, with a natural change in the daily cycle. The research concept was approved by the local ethics committee (protocol No. 12 of 07/12/2019). The contents and manipulations with animals were under generally accepted standards of experimental ethics (Directive 2010/63/EU of the European Parliament and of the council on the protection of animals used for scientific purposes, September 22, 2010).

2.2. Test-objects

The test-objects in this study were ethanol and aqueous extracts of the leaves of European mistletoe (*Viscum album* L., Santalaceae). Samples of plant materials were obtained from two host plants: pear (*Pyrus communis* L., Rosaceae) and black poplar (*Populus nigra* L., Salicaceae). The raw materials procurement was carried out on the Krasnodar region territory (Russia; 44.7713, 39.8788 and 44.5204, 38.0926). The identification of raw materials was carried out by specialists of the Department of Pharmacognosy with a course in the technology of herbal remedies (Head of the Department Dr. of science (Pharm.) DA. Konovalov). Ethanol in various concentrations (95, 70 & 40 %), as well as purified water, were used as extractants. Additionally, leaf samples of host plants were extracted. A total of 16 extracts were obtained.

2.3. Extraction

One g (precise weight) of the crushed raw material was placed in a 100-ml round-bottom flask with a thin grind, 30 ml of ethyl alcohol in different concentration (or water) was added, connected with the reflux condenser and heated in a boiling water bath for 1 hour. After cooling, the resulting extract was filtered through a filter paper into a 100-ml volumetric flask. Extraction was repeated twice under the conditions described above. The extract were filtered through the same filter into the same volumetric flask. After cooling, the volume was adjusted with ethyl alcohol (or water) to the mark and mix [17].

Previously, the presence of flavonoids (quercetin), oxycinnamic acids, and amino acids (glutamic and aspartic acids) was detected in the studied extracts.

2.4. Study design

The first stage of this work was the investigation of the amino acid composition and the study of the acute toxicity of the test-extracts. Acute toxicity was evaluated in 80 mice, divided into 16 groups by 5 animals. Next, we evaluated the effect of the test-objects on the level of physical performance of animals after a single administration (screening test). During the screening test, 16 groups of animals were formed (n = 10 each group), the test-extracts were administered P.O. at a dose of $^{1}/_{50}$ of LD_{50} (or, in

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the absence of animal death, the maximum administered dose). Based on the obtained results, extracts were selected for further work, upon administration of which the level of physical performance of mice increased most significantly. Further, the effect of the test-extracts on the level of animal endurance (n = 10 in the group) during course administration (10 days) was evaluated. In this case, the test-objects were administered according to a scheme similar to the screening test (P.O. at a dose of $^1/_{50}$ from LD_{50}). After testing, the animals were decapitated and biomaterial was taken - skeletal muscle (*m. quadriceps femoris*), in which pro/antioxidative balance indicators, apoptotic reaction rates, mitochondrial function parameters (ATP - generating activity, glycolysis intensity, ATP concentration) were investigated, as well as blood serum was taken too (estimated lactic acid concentration) (Fig. 1). Investigated groups: NC - negative control group of animals; VAEPC95 - a group of animals that received 95 % ethanol extract of European mistletoe collected from pear; VAEPC70 - a group of animals that received 70 % ethanol extract of European mistletoe collected from pear; VAEPC40 - a group of animals that received 40 % ethanol extract of European mistletoe collected from pear; VAEPCW - a group of animals that received an aqueous extract of European mistletoe collected from pear; VAEPN95 - a group of animals that received 95 % ethanol extract of European mistletoe collected from black poplar; VAEPN70 - a group of animals that received 70 % ethanol extract of European mistletoe collected from black poplar; VAEPN40 - a group of animals that received 40 % ethanol extract of European mistletoe collected from black poplar; VAEPNW - a group of animals that received an aqueous extract of European mistletoe collected from black poplar; PC95- 95 % ethanol extract from the pear leaves; PC70- 70 % ethanol extract from the pear leaves; PC40- 40 % ethanol extract from the pear leaves; PCW - aqueous extract from the pear leaves; PN95- 95 % ethanol extract from black poplar leaves; PN70- 70 % ethanol extract from black poplar leaves; PN40- 40 % ethanol extract from black poplar leaves; PNW - water extract from black poplar leaves.

2.5. Amino acids determination

The amino acid composition of the analyzed samples was evaluated by paper chromatography in the mobile phase: *n*-butanol - acetic acid-water (4:1:3); acetone - water (3:2). Fixed phase: FN-7 grade paper (Germany). Developer: alcohol solution of ninhydrin. Amino acids in the test-extracts were determined by comparing the mobility coefficients of the analyzed samples with standard solutions of amino acids: asparagine, glutamic acid, serine, glycine, alanine, tryptophan and methionine (Sigma-Aldrich) [17].

2.6. Studying of the test-objects: acute toxicity

Evaluation of the "acute toxicity" of the test-extracts was carried out using the generally accepted approach to determining the toxicity of chemical substances in an acute experiment - the "Up and Down" procedure, the main provisions of which are described in the guidelines No. 425 "Oral toxicity assessment of chemical compounds" by the Organization for Economic Co-operation and Development. According to the testing procedure, the study of "acute toxicity" was performed in 2 stages: the limiting and the main test. The studied objects were administered P.O., fractionally, through an atraumatic catheter at a dose of 5000 mg/kg (under the conditions of the limit test). The criterion for stopping the test according to the results of the limit test was the absence of animal death; otherwise, the main test was performed [18].

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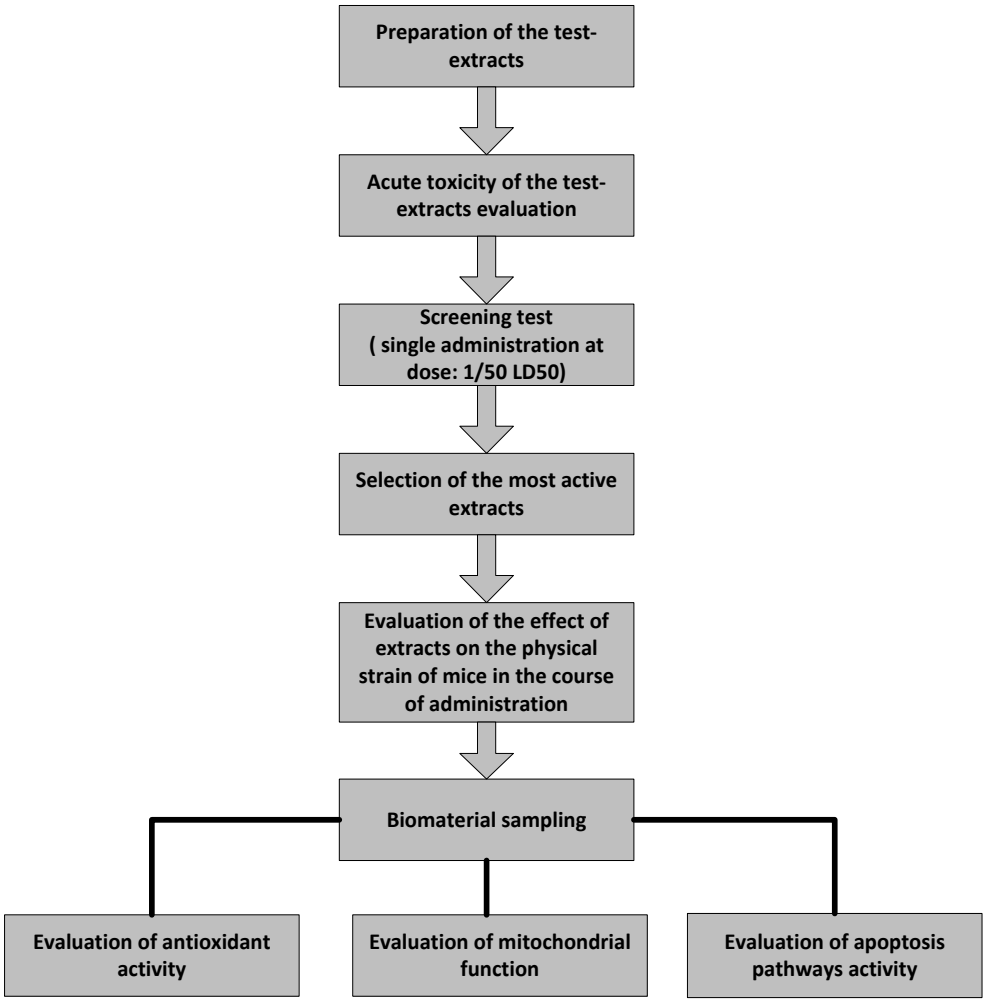


Fig. 1. Study design

2.7. Physical overloads model - forced swimming with a load

"Forced swimming" was carried out in a device consisting of an acrylic cylinder 30 cm high and 10 cm in diameter, with desaturated water at a temperature of 15 ºC. A load equal to 20 % of animal's body weight was attached to the mice tail, after which the animal was placed in the cylinder. Previously, all animals were randomized by swimming time. The test-extracts were administered daily 1 hour before the physical overloads modeling. Swimming was carried out until the exhaustion and refusal of the struggle for life (the animal was at the bottom of the pool for 7 seconds). The swimming time of mice in seconds was recorded [19].

2.8. Biomaterial sampling

The skeletal muscles of animals (*m. quadriceps femoris*) were used as a biomaterial in the work. The muscles were divided into 2 parts: the first was homogenized in a medium: 1 mmol EDTA + 215 mmol mannitol + 75 mmol sucrose + 0.1 % BSA solution + 20 mmol HEPES (pH 7.2), followed by double centrifugation in the modes: 1400 g → 3 min at 4 ºC (supernatant is removed) and 13000 g → 10 min. The resulting secondary supernatant was taken for a

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respirometric analysis. The second part of the biomaterial was homogenized in PBS with a pH of 7.4 in a ratio of 1:7 (homogenate was taken to determine prooxidants) and centrifuged in the mode of 10000 g → 5 min, then the resulting supernatant was removed for ELISA and antioxidant enzyme activity determination. To obtain serum in mice blood was taken by a 2 ml syringe with citrate spraying (from the abdominal aorta). After that, the blood was centrifuged in the mode of 1000 g → 10 min [20].

2.9. Studying of ATP-generating activity and glycolysis intensity

The study was performed according to the SEAHORSE protocol on a laboratory AKPM-01L respirometer (Alfa-Bassens, Russia). During the analysis, the change of oxygen consumption in a medium containing native mitochondria was assessed against the background of the introduction of mitochondrial respiration disconnectors: oligomycin 1 μg/ml; 4-trifluoromethoxy) phenyl) hydrazono) malononitrile (FCCP-1 μM); rotenone - 1 μM; sodium azide - 20 mmol. When studying the intensity of anaerobic processes, the substrate of oxidation was glucose (15 mmol). In this case, the following parameters characterizing the respiratory function of mitochondria were calculated: ATP-generating activity and glycolysis intensity [20].

2.10. Lactic acid concentration evaluation

The concentration of lactate was determined in the enzymatic reaction with the formation of quininomine, the concentration of which is proportional to the content of lactic acid in the sample. Incubation medium: phosphate buffer (pH 6.8), Pipes 50 mmol/L, 4-chlorophenol 6 mmol/L, 4-AAP 0.4 mmol/l, 2000 U/L lactoxydase, U/L peroxidase. The volume of the test sample is 10 μl. Sampling was carried out at 500 nm. Calculation of lactic acid was carried out according to the formula:

$$C = Ex/E0 \times 3.34\ \mu mol/L$$

where Ex: absorbance of the test sample; E0: absorbance calibration sample [18].

2.11. Diene conjugates concentration evaluation

The concentration of diene conjugates (DC) in the homogenate of muscle tissue was determined spectrophotometrically at 233 nm. DC was recovered with a mixture of heptane: isopropanol (1:1). The amount of DC was calculated by the molar extinction coefficient of conjugated dienes at 233 nm by following formula and expressed in nmol/mg protein:

$$X = \text{Absorbance} \times 10/2.2 \times 10^5\ M^{-1}.cm^{-1}$$

Protein content was determined by the Folin method [211].

2.12. Malondialdehyde concentration evaluation

The concentration of malondialdehyde (MDA) was estimated in the muscle tissue homogenate by spectrophotometric method in the condensation reaction with 2-thiobarbituric acid, during which the resulting colored complex has an absorption maximum at 532 nm. In this case, the color of the solution is proportional to the concentration of malondialdehyde. The amount of MDA was calculated by the value of the molar extinction coefficient with following formula:

$$X = \text{Absorbance} \times 10/1.56 \times 10^5\ M^{-1}.cm^{-1}$$

The results were expressed in nmol/mg protein. Protein content was determined by the Folin method [22].

2.13. Catalase activity evaluation

Catalase activity was determined in the skeletal muscle supernatant spectrophotometrically by the rate of hydrogen peroxide destruction. The amount of hydrogen

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peroxide was determined in reaction with a 4 % solution of ammonium moly date. The color intensity of the reaction product was evaluated at 410 nm. Catalase activity was calculated by the difference between the extinctions of the experimental and blank samples, using the molar extinction coefficient of hydrogen peroxide by following formula and expressed in units/protein mg:

$X = \text{Absorbance} \times 10/22.2 \times 10^3\ mm^{-1}.cm^{-1}$

Protein content was determined by the Folin method [23]

2.14. Superoxide dismutase activity evaluation

The activity of superoxide dismutase (SOD) was evaluated by the xanthine-xanthine oxidase method based on the reaction of the dismutation of the superoxide radical formed during the oxidation of xanthine and reduction of 2-(4-iodophenyl)-3-(4-nitrophenol)-5-henyltetrazolium chloride. The incubation medium contained: xanthine 0.05 mmol/l; 2-(4-iodophenyl)-3-(4-nitrophenol)-5-phenyltetrazolium chloride 0.025 mmol/L; EDTA 0.94 mmol/L, xanthine oxidase 80 U/L, CAPS - 40 mmol/L. The optical density of the mixture was recorded at 505 nm. SOD activity was expressed in units/protein mg. Protein content was determined by the Folin method [24].

2.15. Glutathione peroxidase activity evaluation

Glutathione peroxidase (GPx) activity was determined in the supernatant of muscle in the conjugated glutathione reductase reaction according to the decrease in NADPH. The incubation medium contained: 1 mmol/L EDTA, 50 mM K, Na-phosphate buffer, pH 7.4; 1 unit/ml glutathioreductase; 20 mmol/L NADPH; 1 mmol/L GSH; 30-60 μg of protein per 1 ml of medium. The optical density of the mixture was recorded at 340 nm. The reaction was started by adding a substrate (cumene hydroperoxide-1.5 mmol/L) and was carried out at a temperature of 25 ºC. GPx activity was expressed in units/protein mg. Protein content was determined by the Folin method [25].

2.16. ELISA study

In the study, the concentrations of ATP, caspase-3, and apoptosis-inducing factor (AIF) were determined by ELISA in the supernatant of muscle tissue. In the work, we used standard species-specific reagent kits for ELISA manufactured by *Cloud clone*. The preparation of samples and the analysis progress corresponded to the instructions attached to each set.

2.17. Statistical Analysis

Statistical processing of the obtained results was performed using the STATISTICA 6.0 application software package (StatSoft, USA). Data were expressed as M (mean) ± SEM. A comparison of means groups was carried out by the method of one-way analysis of variance with the post-processing Newman-Keulse test.

3. Results

3.1. Amino acid composition

Analysis of the amino acid composition of European mistletoe extracts was carried out in aqueous extract. In the course of this block of experimental work, it was found that glutamic and aspartic acids, serine, glycine, alanine, tryptophan, methionine are present in the analyzed samples. The results are presented in Table 1.

3.2. Acute toxicity

It was found that under the conditions of the ultimate test, when the mice received extracts of both European mistletoe extracts and extracts from the host plants leaves at a dose of 5000 mg/kg, no animal deaths were noted. After the last administration of the test-extracts, the animals occupied a lateral position, an increase in the number of urination acts, and a decrease in feed and water intake were also noted. Since,

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during the ultimate test, no death of mice was noted, we did not proceed to the main test. At the same time, the LD_{50} value for the test-objects was more than 5000 mg/kg. Thus, according to the GSH classification, the test-extracts can be attributed to the 5th class of toxicity.

Table 1. Amino acid composition of the test-aqueous extracts from European mistletoe (the mobility coefficients)

Standard samples	The mobility coefficient of water extracts			
	***Viscum album* L. from poplar**	***Viscum album* L. from pear**	***Populus nigra* L.**	***Pyrus communis* L.**
Aspartic acid	0.24 ± 0.01	0.24 ± 0.01	0.25 ± 0.01	0.25 ± 0.01
Glutaminic acid	0.29 ± 0.01	0.28 ± 0.02	0.30 ± 0.02	0.30 ± 0.01
Serine	0.38 ± 0.02	0.38 ± 0.02	0.38 ± 0.02	0.39 ± 0.02
Glycine	0.44 ± 0.02	0.43 ± 0.02	-	-
Alanine	0.47 ± 0.02	0.47 ± 0.02	0.46 ± 0.02	0.45 ± 0.02
Thryptophan	0.56 ± 0.02	0.54 ± 0.02	0.56 ± 0.02	-
Methionine	0.65 ± 0.03	0.63 ± 0.03	0.63 ± 0.03	0.64 ± 0.03

3.3. Evaluation of the physical performance of mice after a single administration

During this block of the experimental study, it was found that in the negative control group of animals (NC), the duration of swimming under the conditions of a single exhaustive test was not statistically significant to the baseline indicator of this group (Fig. 2). At the same time, against the background of a single administration of 40 % ethanol extracts of European mistletoe collected from pear (VAEPC40) and black poplar (VAEPN40), the physical performance level of mice increased in comparison with the baseline one by 63.4 % ($P < 0.05$) and 49.9 % ($P < 0.05$), respectively. Besides, a single administration of European mistletoe extracts obtained by extraction with 70 % ethanol, increased the swimming time of mice relative to the baseline level of physical performance by 50.8 % ($P < 0.05$) and 45.53 % ($P < 0.05$) when using the extracts of European mistletoe, collected from pear (VAEPC70) and black poplar (VAEPN70), respectively (Fig. 2). It should be noted that, against the background of the administration of the remaining test-extracts of European mistletoe, as well as extracts obtained from the host plants leaves, the duration swimming of animals under conditions of a single exhaustive test did not change statistically significantly concerning the baseline physical strain (Fig. 2). Thus, for further studies, the 40 % and 70 % European mistletoe extract were selected.

3.4. Evaluation of the physical performance of mice with the course application

The duration of the study was 10 days. The use of the test VAEPN70 extract helped to maintain the level of physical activity of mice. The duration of animals swimming on the 10^{th} day of the experiment exceeded the physical strain of mice NC group (10^{th} day of the study) by 2.7 times ($P < 0.05$). Similar results were obtained when animals were treated by VAEPC70 extract. (Fig. 3). Against the background of the introduction of VAEPN40 extract to animals, the swimming time of mice on the 10^{th} day of the experiment increased by 1.79 times ($P < 0.05$) compared with the baseline of this group of animals and by 3.4 times ($P < 0.05$) relative to the physical strain index of the NC

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group mice on the 10th day of the study (Fig. 3). The use of the test VAEPC40 mistletoe extract contributed to the increase in the swimming time of animals in comparison with the NC group. Also, the duration of animals swimming that were treated by VAEPC40, on the 10th day of the study was higher in comparison with similar indicators of mice treated with extracts of VAEPN40; VAEPN70 and VAEPC70 48.8 % ($P < 0.05$); 85.2 % ($P < 0.05$) and 108.6 % ($P < 0.05$), respectively (Fig. 3).

3.5. Influence of the test extracts-leaders on the change in the pro/antioxidant balance in the animals muscle tissue after suffering exhausting physical overloads

As a result, it was found that in the NC group, after physical overloads modeling relatively intact animals, inhibition of the activity of endogenous antioxidant defense enzymes SOD,

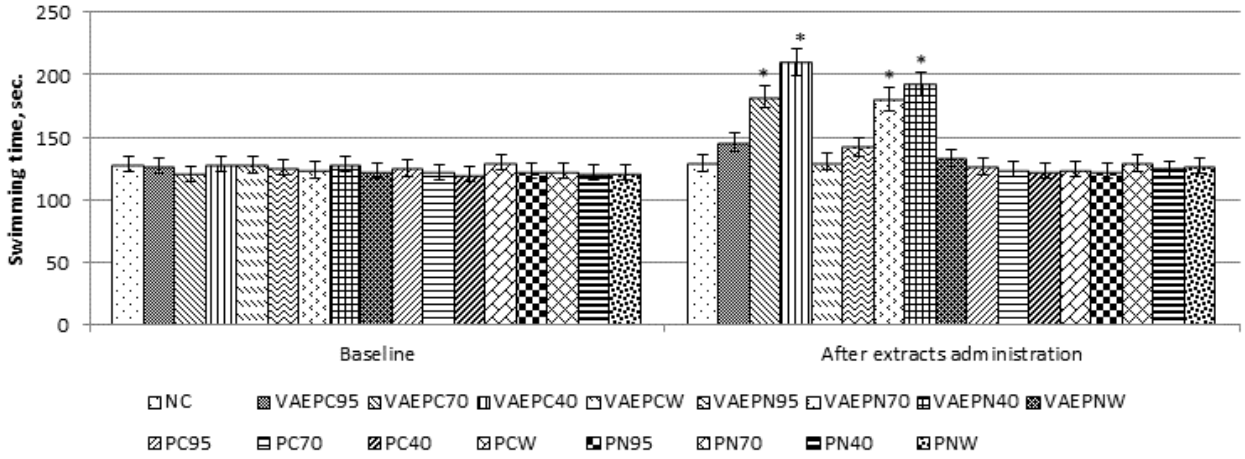


Fig. 2. The effect of the test-extracts on the physical performance of mice in the conditions of the «forced swimming» test after a single administration, Note: * Statistically significant relative to the baseline

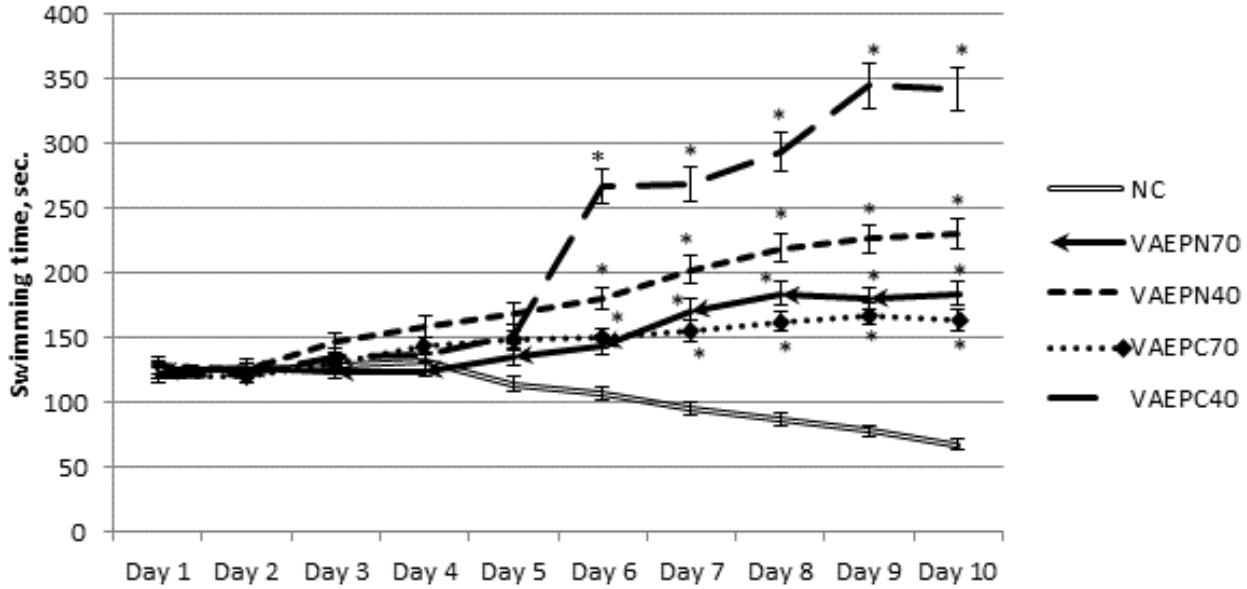


Fig. 3. The effect of the test extracts-leaders on the mice swimming time in the conditions of the «forced swimming test» at a course administration. * Statistically significant relative to the Negative Control group of animals (NC)

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GPx, and catalase was observed. At the same time, the NC group of mice showed an increase in the activity of lipid peroxidation processes, as evidenced by an increase in the concentration of DC and MDA (Table 2). Thus, the course administration to animals of 70 % ethanol mistletoe extracts VAEPC70 and VAEPN70 did not significantly affect the change in the pro / antioxidative balance in the animal's muscles (no statistically significant differences for the NC group of mice were found). At the same time, the use of VAEPN40 extract increased the activity (compared with the NC group of mice) of SOD, GPx, and catalase with a decrease in the content of MDA and DC (Table 2). Against the background of the administration of VAEPC40 extract to mice, an increase in the activity of antioxidant enzymes SOD, GPx, and catalase in muscle tissue compared with the NC values of the animal group by 38.3 % ($P < 0.05$); 2.3 times ($P < 0.05$) and 7.5 times ($P < 0.05$), respectively was observed, while the content of MDA and DC in mice treated by VAEPC40 relative to the NC group of animals decreased 3.1 times ($P < 0.05$) and 2, 5 times ($P < 0.05$), respectively (Table 2).

Table 2. The effect of the test extracts-leaders on the change in the pro / antioxidant balance in the animals muscle tissue after physical overloads

Group	IA	NC	VAEPC40	VAEPA40	VAEPA70	VAEPC70
SOD (U/mg)	600.5 ± 7.12	303.7 ± 6.32$^{\#}$	419.21 ± 6.08*	409.9 ± 6.74*	319.86 ± 7.49	317.8 ± 5.42
GPx (U/mg)	602.6 ± 5.94	289.1 ± 4.62$^{\#}$	671.33 ± 9.67*	644.87 ± 11.07	290.26 ± 11.64	300.97 ± 7.60
Catalase (U/mg)	0.863 ± 0.01	0.163 ± 0.01$^{\#}$	1.229 ± 0.02*	0.825 ± 0.05*	0.247 ± 0.02	0.206 ± 0.09
MDA (nmol/mg)	1.4 ± 0.52	10.2 ± 0.62$^{\#}$	3.24 ± 0.15*	4.27 ± 0.46*	8.71 ± 0.29	8.66 ± 0.25
DC (nmol/mg)	1.8 ± 0.69	8.8 ± 0.31$^{\#}$	4.21 ± 0.36*	8.39 ± 0.61*	9.63 ± 0.62	8.41 ± 0.43

IA: Intact Animals; SOD: Superoxide Dismutase: GPx: Glutathione Peroxidase; MDA: Malondialdehyde; DC: Diene Conjugates; $^{\#}$ Statistically significant relative to intact animals; * Statistically significant relative to the NC group of mice

3.6. Evaluation of the change of the mitochondrial function parameters in the muscle tissue of animals after suffering exhausting physical overloads

VAEPC70 and VAEPN70 extracts did not significantly effect on the change in mitochondrial function under conditions of physical overloads. At the same time, the VAEPN40 test-object administration contributed to an increase in ATP-generating ability compared to the NC group of mice by 6.78 times ($P < 0.05$), as well as a decrease in the intensity of glycolysis by 2.15 times ($P < 0.05$). As a result, the concentration of ATP (Fig. 5) in the muscle tissue of animals treated by VAEPN40 extract increased by 53.8% ($P < 0.05$) relative to the NC group of mice, with a decrease of the lactic acid concentration (Fig. 6) in blood serum by 3.46 times ($P < 0.05$).

Administration of the VAEPC40 test-extract to animals compared to the NC group of mice showed an increase in ATP-generating ability by 9.8 times ($P < 0.05$), accompanied by a decrease in the intensity of anaerobic processes (Fig. 4) by 3.3 times ($P < 0.05$). At the same time, the concentration of ATP (Fig. 5) in the muscle tissue of animals treated by VAEPC40 increased by 2 times ($P < 0.05$) relative to the NC group of mice, and the content of lactic acid (Fig. 6) in the blood serum, on the contrary, decreased 4.6 times ($P < 0.05$).

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3.7. Evaluation of the activity change of the apoptotic system in the muscle tissue of animals after suffering exhausting physical overloads

The use of the VAEPN40 test extract contributed to a decrease in the activity of the pro-apoptotic AIF-system by 2.1 ($P < 0.05$) times, caspase-3 - by 88.2 % ($P < 0.05$). At the same time, against the background of the administration of VAEPC40 extract to animals, a decrease of the AIF and caspase-3 concentration by 2.28 times ($P < 0.05$) and 2.46 times ($P < 0.05$), respectively was observed. It should be noted that with the course administration of VAEPC70 and VAEPN70 70 % ethanol extracts, the content of AIF and caspase-3 in muscle tissue of animals did not statistically significantly different from the similar parameters of the NC group of mice (Fig. 7).

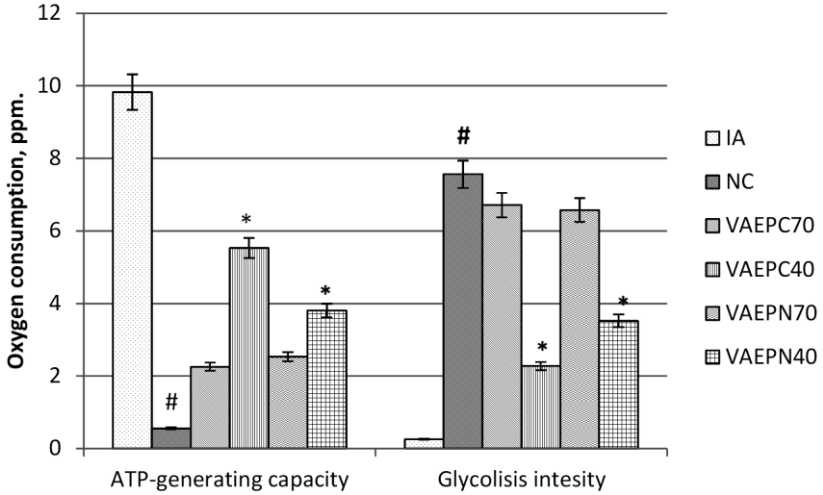


Fig. 4. Change in ATP-generating activity and the intensity of anaerobic processes in the mice muscle tissue treated by the test extracts-leaders. # Statistically significant relative to intact animals; * Statistically significant relative to the negative control group of animals (NC); IA: Intact Animals

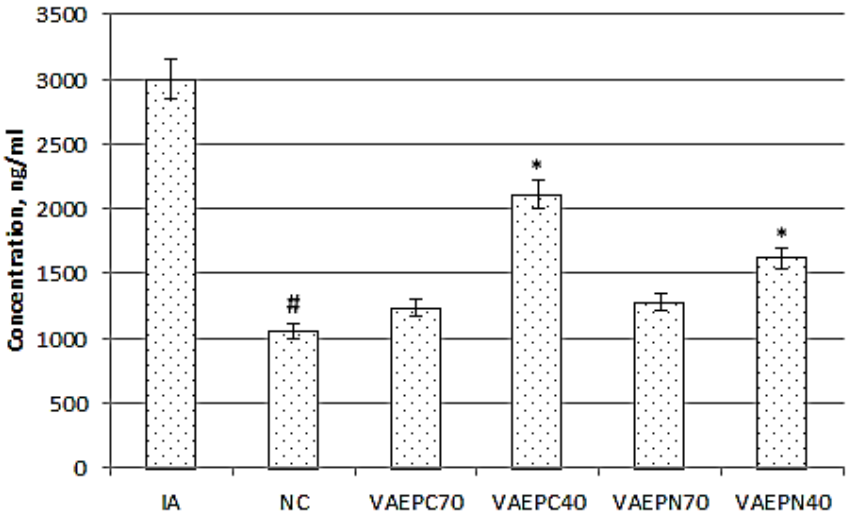


Fig. 5. Changes in the concentration of ATP in the mice muscle tissue treated by the test extracts-leaders under conditions of physical overloads. # Statistically significant relative to intact animals; * Statistically significant relative to the negative control group (NC) of animals; IA: Intact Animals

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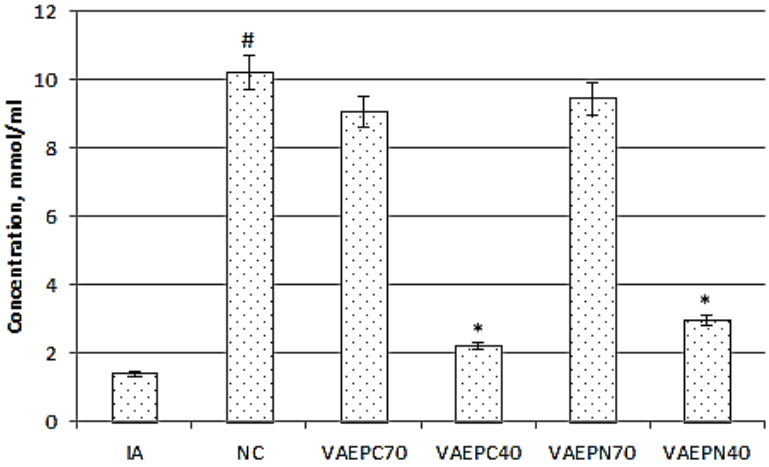


Fig. 6. Change of the lactic acid concentration in the blood serum of mice treated by test extracts-leaders under conditions of physical overloads. # Statistically significant relative to intact animals; * Statistically significant relative to the negative control group of animals (NC); IA: Intact Animals

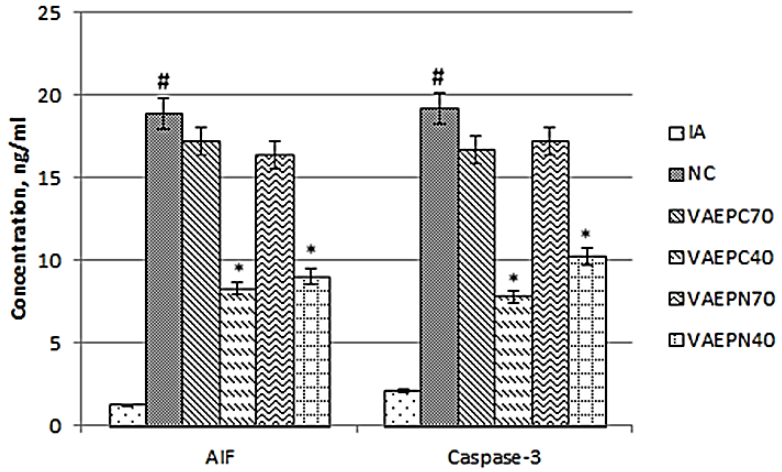


Fig. 7. Change of the apoptosis-inducing factor and caspase-3 concentration in the skeletal muscle supernatant of mice treated by test extracts-leaders under conditions of physical overloads. # Statistically significant relative to intact animals; * Statistically significant relative to the negative control group of animals (NC); IA: Intact Animals

4. Discussion

Stress is a physiological protective reaction to stimulant; however, excessive stress exposure can lead to disruption of homeostasis and maladaptation of the organism, decrease in physical strain [26]. Musculoskeletal symptoms of physical fatigue combine factors that limit the activity of striated muscles: the level of blood flow in skeletal muscles, the kinetics of calcium ions, the generation of free radicals, and the intensity of metabolic processes in muscle tissue [27].

In this case, the limiting factor of skeletal muscle activity is a decrease in the level of blood flow in the muscle tissue. It is known that actively working muscle tissue can consume about 85 - 90 % of the oxygen accumulated by arterial blood during a single cardiac cycle [28] When this indicator is reduced to 50 %, irreversible changes occur in the skeletal muscle

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associated with a disorder of metabolic pathways, activation of oxidative stress and apoptosis, which suggests a significant role of optimal blood supply to skeletal muscles in the pathogenesis of muscle fatigue [29]. At the same time, the leading role in maintaining the proper level of muscle blood flow is assigned to the vascular endothelium [30]. Vascular Endothelium is a thin monolayer of specialized cells lining the lumen of blood vessels, which is a key regulatory link between blood and tissues. Under conditions of intense muscle activity, the turbulent blood flow created by increasing cardiac output and heart rate damages the endothelial lining, especially in the areas of arterial bifurcation, thereby forming a pathological process called endothelial dysfunction and associated with NOS activity [31].

Under conditions of intensive muscle work, there is a decrease in eNOS activity, due to the depletion of cofactors, there is NO synthesis reaction (tetrahydrobiopterin and NADP). It should be noted that under these conditions, a decrease in NO synthesis is associated with progressive inactivation of eNOS by methylated L-arginine derivatives (ADMA) [32]. The decrease in NO production does not cause a failure of paracrine regulation of muscle blood flow, resulting in compensatory activation of inducible nitric oxide synthase (iNOS), which does not produce significantly higher concentrations (mmol, against nmol generated by eNOS). The resulting excess of nitric oxide undergoes accelerated inactivation with the participation of a number of enzymes with oxygenase activity - NADP oxidases and mitochondrial respiratory chain enzymes that generate a superoxide anion radical [33]. As a result of the reaction interaction of NO and superoxide radical, cytotoxic peroxonitrite is formed, which initiates cellular damage by the type of free-radical oxidation reactions, as a result of which a new pathogenetic mechanism of damage to skeletal muscles is triggered - oxidative stress [34]. In this case, the resulting lipoperoxidant products-malonyldialdehyde and other acylperoxides, initiate secondary damage to the myocytes of the striated muscle, through methylation and the formation of DNA adducts, which in turn leads to increased destruction of muscle tissue [35].

It is worth noting that developing oxidative stress is directly associated with mitochondrial dysfunction and increased generation of reactive oxygen species by mitochondria that inactivate NO [36]. Functional mitochondrial imbalance occurs when the level of muscle blood flow decreases to a critical level. In this case, insufficient blood supply to skeletal muscles leads to the formation of two subpopulations of mitochondria: SSM and IFM which play a different role in the pathogenesis of muscle tissue damage [37].

Mitochondria of the SSM type are the main intracellular source of reactive oxygen species. It was found that in the mitochondria of the SSM family, in contrast to the IFM subpopulation, there is a faster oxidation of substrates in complexes I and II and III, without changing the oxygenation in the I complex, which leads to the termination of redox reactions of the mitochondrial respiratory chain, redirecting the oxygen flow towards the formation of ROS at the level of the second complex, thereby reducing the coupling of oxidation and phosphorylation, and ATP synthesis [38]. It is quite important that the activity of ATP synthase (complex V) decreases in the mitochondria of the SSM type, and the functional properties of NADP oxidase increase, which leads to the formation of intermediates of acidic glucose oxidation reactions, for example, lactic acid [39]. Thus,

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muscle fatigue with physical performance is a complex pathogenetic process, the main chains of which can be eliminated by the use of adaptogenic agents [40]. It is known that adaptogens are usually represented by substances of plant origin. The adaptogenic properties of Ginseng, Rhodiola Rosea, and Schisandra Chinensis are widely known. Having a multifactorial effect on the human body, adaptogens have a regulatory type of action aimed at restoring the functions of the body. In addition, it should be noted that adaptogens have low systemic toxicity [41]. This study focused on assessing the potential adaptogenic properties of extracts obtained from European mistletoe. Since the pharmacological activity of extracts from mistletoe is variable and depends on the type of host plant [42], ethanol (extractant: 95 %; 70 %; 40 % ethanol) and aqueous extracts of mistletoe collected from pear and black poplar were studied in this work.

The study showed that all the test-extracts may have an optimal toxicological profile, since for these objects the LD_{50} value was more than 5000 mg/kg (5^{th} toxicity class according to GSH classification). Further pharmacological screening revealed that the greatest impact on the level of physical performance of mice under forced swimming test conditions was exerted by a single use of 40 % and 70 % ethanol extracts (extracts-leaders), while a single administration of 95 % ethanol and water European mistletoe extracts, as well as extracts obtained from leaves of host plants, did not significantly affect the swimming time of mice. At the same time, the use of 40 % extracts had a more pronounced effect on the level of physical activity of animals during the course application, and the most effective was the administration of 40 % ethanol European mistletoe extract collected from the pear. Among the potential possible mechanisms for the implementation of adaptogenic action, the antioxidant properties of the extracts-leaders were studied. It is known that oxidative stress is one of the trigger mechanisms for the development of muscle fatigue. Besides, an increase in the generation of free radicals during intense physical exertion can impair skeletal muscle recovery processes. Moreover, the increased concentration of free radicals leads to dysfunction of the antioxidant systems of the cell - antioxidant protection enzymes (SOD, catalase, peroxidase), which intensifies the oxidation of lipids, proteins, and nucleic acids [43]. In the course of the work, it was found that the course administration of 40 % European mistletoe extracts white reduced the manifestations of oxidative stress and restored the activity of antioxidant enzymes. It is worth noting that, against the background of the administration to animals of 40 % European mistletoe ethanol extract collected from the pear, the concentration of MDA and DC decreased, the normalization of the activity of SOD, catalase and glutathione peroxidase to a greater extent than with the other extracts-leaders was observed.

It is known that during excessively intense physical work, the main source of macroergic compounds for skeletal muscle is anaerobic metabolism reactions [44]. However, the intensification of glycolysis reactions is not able to adequately provide energy to the working skeletal muscle, as a result of which there is a deficiency of ATP and the accumulation in the cell of unoxidized intermediates, for example, lactic acid [45]. The resulting hyperlactatemia and metabolic acidosis sharply limit the adaptive potential of striated muscles, which in turn contributes to muscle fatigue [46]. In this study, it was found that the course administration of 40 % ethanol extracts contributed to a decrease in the intensity of anaerobic processes, as well as an

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increase in the ATP-generating capacity of mitochondria, which ultimately led to an increase of the ATP concentration in skeletal muscles and leveled hyperlactatemia. At the same time, against the background of the administration of 70 % European mistletoe ethanol extracts, no significant change in mitochondrial function was observed in mice. A decrease in the level of ATP in the cell, in addition to restricting muscle contractility, leads to the activation of apoptotic reactions in striated myocytes [47]. Apoptosis is a physiological reaction aimed at eliminating damaged cells and limiting alteration. At the same time, an uncontrolled apoptotic cascade leads to the death of functionally normal cells, which under conditions of excessive physical overloads can lead to muscle fatigue and injuries of skeletal muscles [47]. A significant role in muscle damage by the apoptotic mechanism is played by both caspase-dependent and caspase-independent apoptosis reactions [48]. The effector system in caspase-dependent apoptotic reactions is caspase-3, while the caspase-independent cascade largely depends on the activity of the apoptosis-inducing factor [49]. We found that 40 % European mistletoe ethanol extracts collected from pear and black poplar under intense physical overloads in mice reduce the intensity of reactions of both caspase-dependent and caspase-independent apoptosis, as evidenced by a decrease of caspase-3 and apoptosis-inducing factor concentration in the supernatant of the animal's skeletal muscle.

5. Conclusion

Physical overloads are a fairly energy-intensive process, leading to a breakdown in the constancy of the internal environment of the organism. The study showed that the use of 40 % ethanol extracts from European mistletoe (host plants: pear and black poplar) under experimental conditions contributed to an increase in the physical performance of animals, probably due to the normalization of pro / antioxidative balance and energy metabolism, which suggests the prospect of further studying this object for adaptogenic activity. This study is limited to investigating the effect of European mistletoe extracts on the physical performance of mice, however, the dose-dependent effect of the extracts, as well as studying the pharmacological effect of the European mistletoe extracts under experimental stress, temperature changes, and immunodeficiency, can be of undoubted scientific and practical interest.

Author contributions

DI. P. was involved in conducting experiments, processing data, writing a manuscript and development of the research concept; SL. A. & NM. C. were involved in obtaining the studied extracts and conducting experiments; AV. V. & ET. O. were involved in development of the research concept, literature review, obtaining the studied extracts.

Conflict of interest

The authors declare that there is no conflict of interest.

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How to cite this article: Pozdnyakov DI, Adzhiahmetova SL, Chervonnaya NM, Voronkov AV, Oganesyan ET. Some aspects of the adaptogenic potential of European mistletoe (*Viscum album* L.) extracts under variable physical performance. ***Journal of Medicinal Plants*** 2021; 20(77): 60-78. doi: 10.29252/jmp.20.77.60

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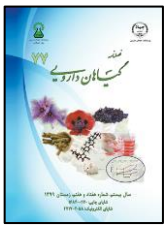
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فصلنامه گیاهان دارویی ۱۳۹۹؛ ۲۰(۷۷): ۶۰-۷۸

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مقاله تحقیقاتی

برخی از جنبه‌های پتانسیل سازگاری عصاره‌های داروش (*Viscum album* L.) تحت عملکرد فیزیکی متغیر

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اطلاعات مقاله

گل‌واژگان:
داروش
Viscum album L.
تیره صندل
عوامل سازگاری
آنتی‌اکسیدان
متابولیسم انرژی
استرس

چکیده

مقدمه: استرس بخشی جدایی‌ناپذیر از زندگی انسان است و منجر به ناسازگاری ارگانیسم می‌شود و نیاز به اصلاح فارماکولوژیکی منطقی دارد. **هدف:** هدف از این آزمایش ارزیابی توانایی سازگاری عصاره‌های داروش بود. **روش بررسی:** مطالعه بر روی موش‌های Balb/c انجام شد. داروش از درخت گلابی و تبریزی جمع‌آوری شد و عصاره‌های اتانولی و آبی آن در دوز ۱۰۰ میلی‌گرم در کیلوگرم (به صورت خوراکی) تهیه گردید. فعالیت فیزیکی بیش از اندازه در آزمون شنای اجباری مدل‌سازی شد. پارامترهای مورد تجزیه و تحلیل عبارت بودند از: مدت زمان شنا حیوانات، تغییر در پارامترهای تنفس میتوکندریایی، غلظت ATP، فعالیت کاسپاز ۳ و فاکتور القا کننده آپوپتوز در عضلات و اسید لاکتیک در سرم خون حیوانات. وضعیت سیستم پیش/ آنتی‌اکسیدانی و سمیت حاد عصاره‌های آزمایش شده نیز مورد بررسی قرار گرفت. **نتایج:** این مطالعه نشان داد که LD_{50} عصاره‌های آزمایشی بیش از ۵۰۰۰ میلی‌گرم در کیلوگرم (به صورت خوراکی) بود. عصاره‌های اتانولی ۴۰ و ۷۰ درصد داروش با یک بار مصرف، بیشترین تأثیر را روی فشار جسمی موش‌ها داشتند. با مصرف عصاره‌های اتانولی ۴۰ درصدی داروش جمع‌آوری شده از درخت تبریزی و گلابی، زمان شنای موش‌ها به ترتیب ۳/۴ و ۵/۰۵ برابر ($P < ۰/۰۵$) افزایش یافت. همچنین، استفاده از عصاره‌های ۴۰ درصدی به عادی‌سازی تعادل پیش / آنتی اکسیدانی، ترمیم متابولیسم انرژی سلول و کاهش شدت واکنش‌های آپوپتوز کمک کرد. **نتیجه‌گیری:** این مطالعه نشان داد که عصاره‌های اتانولی ۴۰ درصدی داروش (گیاهان میزبان: گلابی و تبریزی) به طور بالقوه می‌توانند به عنوان عوامل سازش‌زا استفاده شوند.

مخففها: O.P، خوراکی؛ LD_{50}، دوز کشنده متوسط

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تاریخ دریافت: ۴ خرداد ۱۳۹۹؛ **تاریخ دریافت اصلاحات:** ۱۹ آبان ۱۳۹۹؛ **تاریخ پذیرش:** ۲۴ آبان ۱۳۹۹

doi: 10.29252/jmp.20.77.60

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[DOR: 20.1001.1.2717204.2021.20.77.6.7]

[DOI: 10.52547/jmp.20.77.60]