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ҚАЗАҚСТАН РЕСПУБЛИКАСЫ
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ВЕСТНИК

НАЦИОНАЛЬНОЙ АКАДЕМИИ НАУК
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NAS RK is pleased to announce that Bulletin of NAS RK scientific journal has been accepted for indexing in the Emerging Sources Citation Index, a new edition of Web of Science. Content in this index is under consideration by Clarivate Analytics to be accepted in the Science Citation Index Expanded, the Social Sciences Citation Index, and the Arts & Humanities Citation Index. The quality and depth of content Web of Science offers to researchers, authors, publishers, and institutions sets it apart from other research databases. The inclusion of Bulletin of NAS RK in the Emerging Sources Citation Index demonstrates our dedication to providing the most relevant and influential multidiscipline content to our community.

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THE STUDY OF NEUROMEDIATORY ACTION OF THE COMBINATION DRUG "MEMOFIT" UNDER CHRONIC IMMOBILIZATION STRESS

Abstract. Neuromediatory action of the combination drug "Memofit" has been studied using the parameters of lipid peroxidation products and antioxidant system. POL and antioxidant system were determined by marker indicators: specifically, the level of primary oxidation products – diene conjugates and secondary products – malonic dialdehyde; anti-oxidative systems; catalase activity and superoxide dismutase. Experimental research has been performed in 18 WAG rats with approximate body weight from 210 to 230 g. Stress-modeling action has been studied on the model of neuromuscular tension during 5, 15 and 30 days. Immobilization stress was modeled by keeping rats for 5 hours in plastic cages – plastic boxes. Blood serum was used for investigation. Level of primary oxidation products – diene conjugates (DC) and secondary products – malonic dialdehyde (MDA) and state of antioxidant system has been determined by spectrophotometric method. Based on the POL level parameters, we can make a conclusion, that the tested combination drug "Memofit" decreases TBA-AP and DC parameters only on the 30-th day statistically significant in relation to immobilization stress and reaches to control. The level of catalase at immobilization stress + combination drug "Memofit" is 4.12±0.09 c.u., correspondently, that is statistically significant in relation to the group of animals, that were subjected to immobilization stress 6.23±0.03 c.u. ($P<0.05$). The level of SOD at immobilization stress + combination drug "Memofit" reaches 4.16±0,09 c.u. correspondently, that is statistically significantly in relation to immobilization stress 7.13±0.89 c.u. and control 3.59±0.11 ($P<0.05$).

Key words: neuromediatory action, combination drug, chronic immobilization stress.

Introduction. Life under conditions of psychoemotional loads, constant overfatigue and chronic stress leads to the occurrence of different symptoms that make 10-20 % of people consult a doctor. In our days it is not doubtful, that stress plays a great role in the development of many socially significant diseases, which make quality of life worse and reduce life duration. It is known that stress is recognized as a risk factor of neuroses, neurosis-like borderline cases and psychopathic states. Stress prevention and stress induced processes is the actual direction of medicine and pharmacy. At the present time psychotropic drugs of different pharmacological groups such as sedative, anxiolytic (tranquilizers), antidepressants and neuroleptics are used for prevention and treatment of stress [2, 5].

Standard means of pharmacotherapeutic neuroses treatment are anxiolytic and sedative drugs. Now synthetic tranquilizers, the benzodiazepines derivatives, which have a range of adverse effects that limit their use especially under conditions of continuing working activity connected with professional necessity of attention concentration are used most often. Heavy adverse effects caused by benzodiazepines include: development of drug dependence, suppression of respiratory center, myorelaxation with imbalance and falls, drug addiction, abstinence syndrome etc. Taking into consideration such a wide list of adverse effects, that limit their use, a search of alternative herbal medicinal products without mentioned above adverse effects is actual [1]. One of the perspective directions is the search of effective herbal medicinal products, which contain in their composition a complex of biologically active substances and show a wide spectrum of pharmacological activity.

According to WHO data, 80 % of population gives preference to medicinal preparations of a plant origin. Phytotherapeutic drugs practically do not have contraindications, have a wide spectrum of

therapeutic action and can be used for prophylaxis and treatment both independently and in the complex therapy course for a number of diseases of central nervous system. Therefore, the search of medicinal plants with psychotropic activity, that has low toxicity and do not yield by their pharmacologic effect to modern synthetic drugs represents a great interest [4].

The aim of our research was to study a neuromediatory action of the combined medicine "Memofit", POL and antioxidant system were determined by marker indicators: specifically, the level of primary oxidation products – diene conjugates and secondary products – malonic dialdehyde; anti-oxidative systems; catalase activity and superoxide dismutase.

Materials and methods. Investigations of substances obtaining, finished dosage form and also determinations of technological and microbiologic characteristics for "Memofit" capsules were carried out on the basis of LLC "State Enterprise "GNCLS". Capsules were produced in accordance to general technological scheme. Both active substances and excipients in the solid state in the form of a powder were placed into one of the capsules caps that were tightly closed by the other ones. Solid capsules have a coating that consists of two cylindrical parts, one end of each part is rounded and closed, and the other is open. On the basis of the obtained experimental data the industrial technology for a drug production has been developed and introduced into practice at the LLC "State Enterprise "GNCLS".

With the purpose of development of technical conditions for dietary supplement "Memofit" in Ukraine, determination of such quality parameters as organoleptic characteristics, uniformity of mass (2.9.5) and disintegration for finished dosage form has been performed (2.9.3).

Experimental research has been performed in 18 WAG rats with approximate body weight from 210 to 230 g. Stress-modeling action has been studied on the model of neuromuscular tension during 5, 15 and 30 days [1]. Immobilization stress was modeled by keeping rats for 5 hours in plastic cages – plastic boxes. Animals were divided into 3 groups, 6 animals in each group. Animals of group 1 – intact (conventional condition) were intraperitoneally injected through the probe with 3 % of pure starch paste per os. Animals of group 2 were exposed to stress by the way of immobilization for 5 hours and were intraperitoneally injected through the probe with 3 % starch paste per os. Animals of group 3 were intraperitoneally injected per os with 3 % starch paste containing tested combined medicine "Memofit" once daily 1 hour prior to the stress exposition.

Animals of all groups were decapitated under ether anesthesia 5 hours after immobilization stress, in other words – against the background of maximal stress exposition. Blood serum was used for investigation, in the course of POL investigation the blood serum was determined, namely: level of primary oxidation products – diene conjugates (DC) and secondary products – malonic dialdehyde (MDA) with spectrophotometry method [7,8]. State of antioxidant system has been determined by spectrophotometric method: namely, catalase activity and superoxide dismutase (SOD) [9,10]. To detect changes in parameters to be examined, these levels were estimated in control and test animals after 5, 15 and 30 days, respectively.

Neuromediatory action of the combination drug "Memofit" has been studied using the parameters of lipid peroxidation products and antioxidant system because lipid peroxidation (POL) is a primary reaction in the chain of physico-chemical transformations, that lead to destruction of lipoproteid complex of membranes and break their transport functions, and also oppress processes of energy generation, that results in decreasing of cells vital activity. At the same time these processes are the most significant for adaptive renovation and reparation of the functioning structures, lipoproteid membranes, increasing of capacity and buffer capacity of redox-system, and therefore, increasing of fermentation and non-fermentation antioxidant activity (AO-protection) and also in the fine regulation of reactions (POL) in the membrane structures due to functioning of mechanisms that control content of active oxygen radicals, lipid peroxides and catalysts of peroxidase reactions [11].

POL induction takes place due to different disorders of organism functions on conditions of pathology and stress.

In case of overaccumulation of POL products in the organism, a syndrome of lipid peroxidation develops, that involves such pathological components as damage of membrane lipids, lipoproteids and proteins, enzymes inactivation, disorder of cell division and phagocythosis, decreasing of endocrine and immune systems reactivity that results in changing of structural-functioning organization of membranes.

Regulation of excessive formation of lipoperoxides is carried out by means of antioxidant system (AOS), that is composed of antioxidants (AO) localized both in hydrophobic membranous (tocopherol) and in hydrophilic intracellular and extracellular (thiol compounds, selenium derivatives, glutathione system) media, and also in two main groups of enzymes: superoxide dismutase (SOD) and catalase.

AOS provides neutralization by means of cells of free radicals and cellular homeostasis supporting. Distinctive features of the AOS functioning is the unidirectionality of its regulating action, serious consequences of its even short-term insufficiency that results in the biopolymers and cellular membranes damage. At the same time the balance under the action of different endogenic and exogenic factors between AOS and POL inside cells can be broken due to either reduction of antioxidant level or hyper-production of free radicals. The term oxidative stress (OS) was given to this state [6].

Results of pharmacological action study for the combined medicine "Memofit" on lipids peroxi-dation: diene conjugates (DC) and malondialdehyde (MDA) are given on figures 1 and 2.

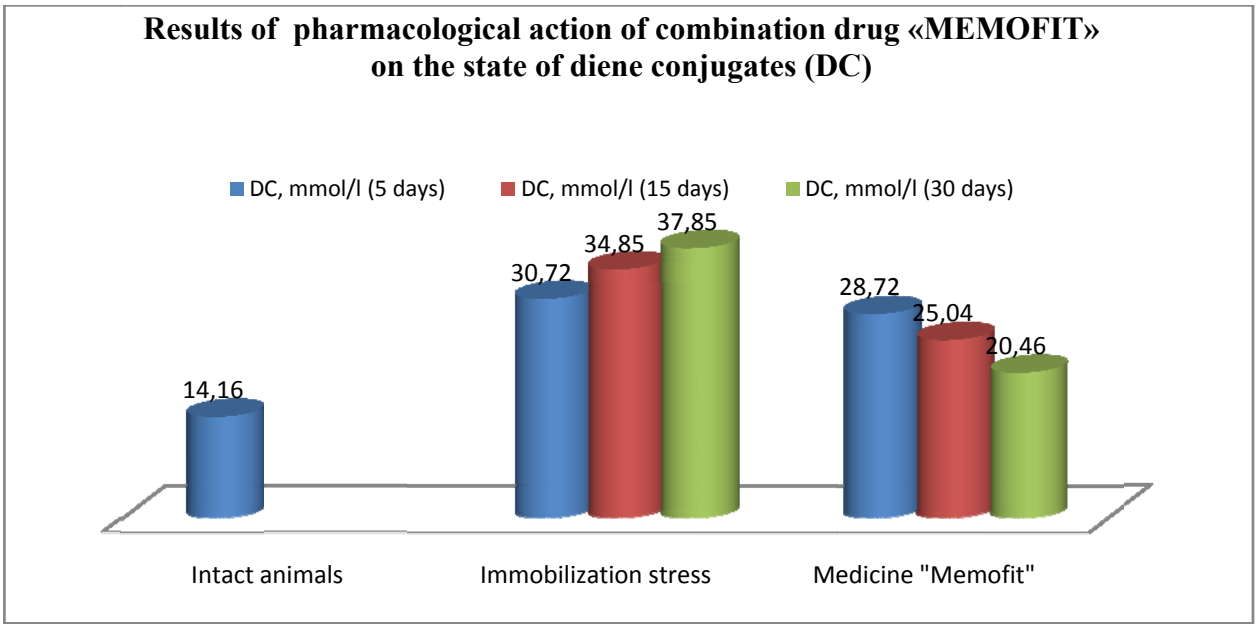

Figure 1

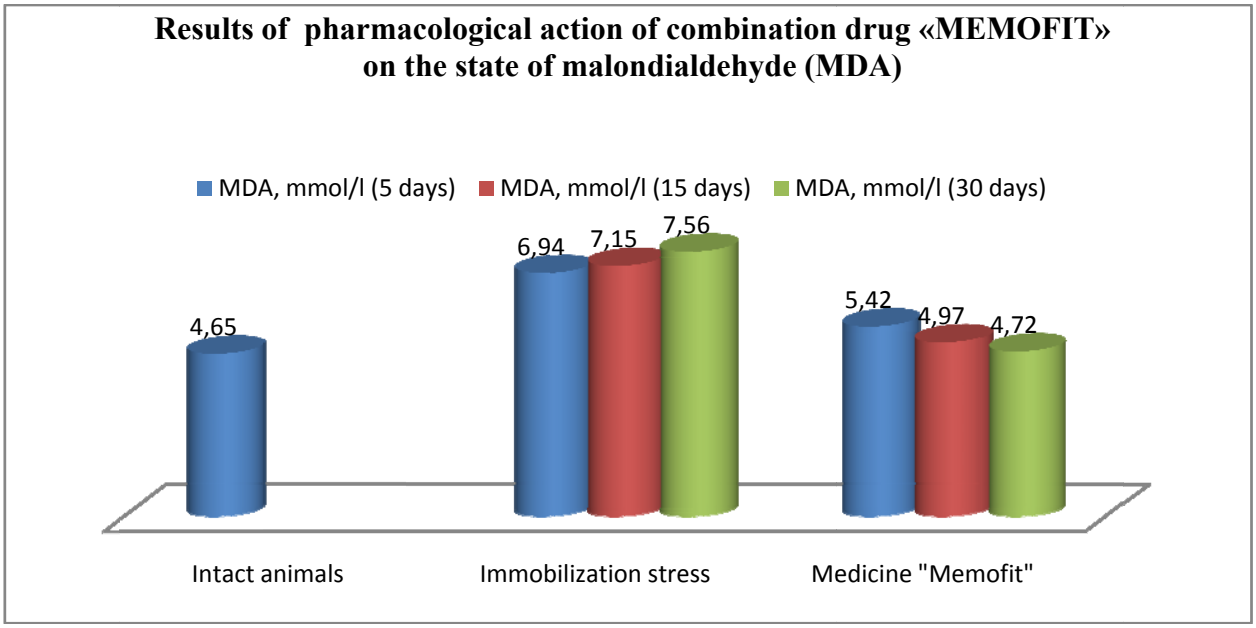

Figure 2

State of POL was determined by the quantity of peroxidation products: DC and TBA – AP, which for intact animals were 14 ± 0.64 mmol/l and 4.65 ± 0.1 mmol/l, correspondently. Figures 1 and 2 show that these parameters increase significantly at immobilization stress on the fifth day. DC level reaches 30.72 ± 1.06 mmol/l that is twice as bigger than the norm, TBA – AP reaches 6.94 ± 0.1 mmol/l, that is 1.5 times as bigger than the control. The DC level on the 15-th day reaches 34.85 ± 0.85 mmol/l, that is 2.5 times as bigger than the norm, TBA – AP reaches 7.15 ± 0.1 mmol/l, that is twice as bigger than the control. The DC level on the 30-th day reaches 37.85 ± 0.12 mmol/l, that is three times bigger than the norm, TBA – AP reaches 7.56 ± 0.78 mmol/l, that is twice as bigger than the control.

Figures1 and 2 show that on the 5-th and 15-th day, level of POL parameters, namely DC and TBA – AP after the use of the combination drug "Memofit" reduces these parameters in 1.2 and 1.7 times, correspondently, that is statistically significant in relation to immobilization stress, but does not reach to the control level.

It is only on the 30-th day that the tested combination drug "Memofit" decreases its DC and TBA – AP levels statistically significant to immobilization stress and reaches control. Thus, DC level on condition of immobilization stress + combination drug "Memofit" is 20.46 ± 0.16 mmol/l correspondently, that is statistically significant in relation to the group of animals, which were subjected to immobilization stress 37.85 ± 0.12 ($P<0.05$).

Level of TBA – AP at immobilization stress + the tested combined medicine "Memofit" is 4.72 ± 0.21 mmol/l correspondently, that is statistically significant in relation to immobilization stress 7.56 ± 0.78 mmol/l ($P<0,05$).

Therefore, based on the POL level parameters, we can make a conclusion, that the tested combination drug "Memofit" decreases TBA-AP and DC parameters only on the 30-th day statistically significant in relation to immobilization stress and reaches to control.

The study results of pharmacological action of the combination drug "Memofit" on the state of antioxidant system (AOS) that is composed of the two main groups of enzymes: superoxide dismutase (SOD) and catalase are given in the figure 3 and 4.

State of antioxidant system was determined by the quantity of catalase products and superoxide dismutase (SOD), which in intact rats are 5.10 ± 0.13 c.u. and 3.59 ± 0.11 c.u. correspondingly.

Figure 3 and 4 demonstrate that at immobilization stress these parameters increase significantly. The catalase level at immobilization stress on the 5-th day reaches 5.88 ± 0.26 c.u. that statistically significantly exceeds the norm ($P<0.05$), SOD reaches 6.93± 0.49 c.u. that is 2 times bigger than the norm. The level of catalase on the 15-th day reaches 6.03 ± 0.21 c.u. that is one and a half times bigger than the

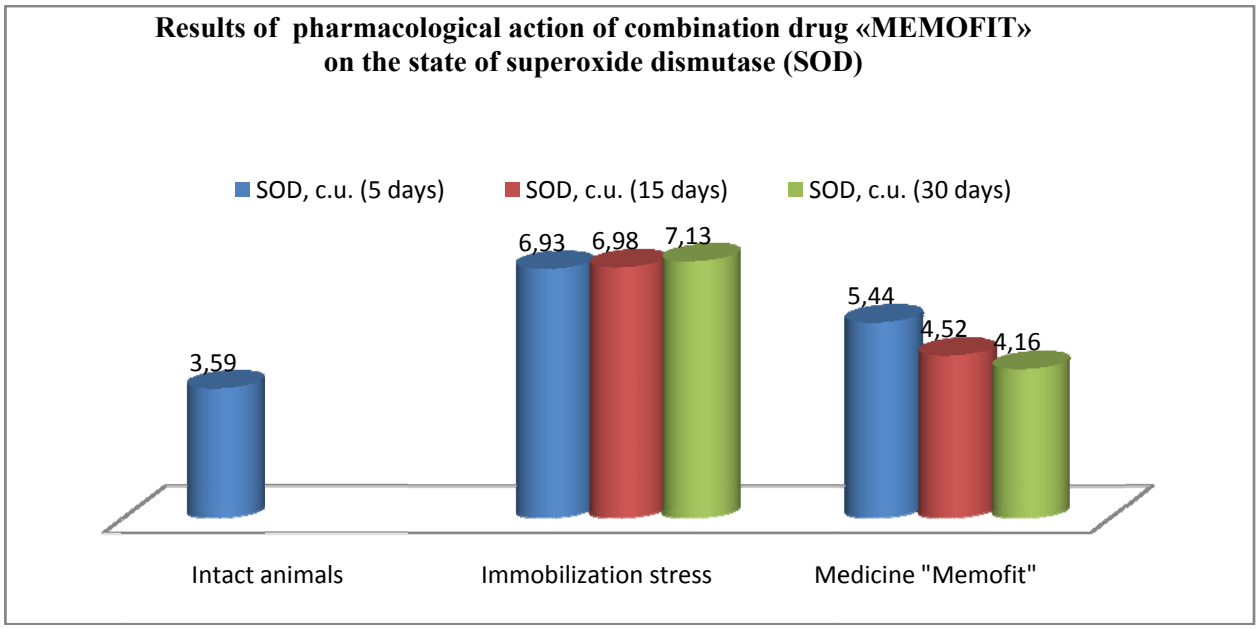

Figure 3

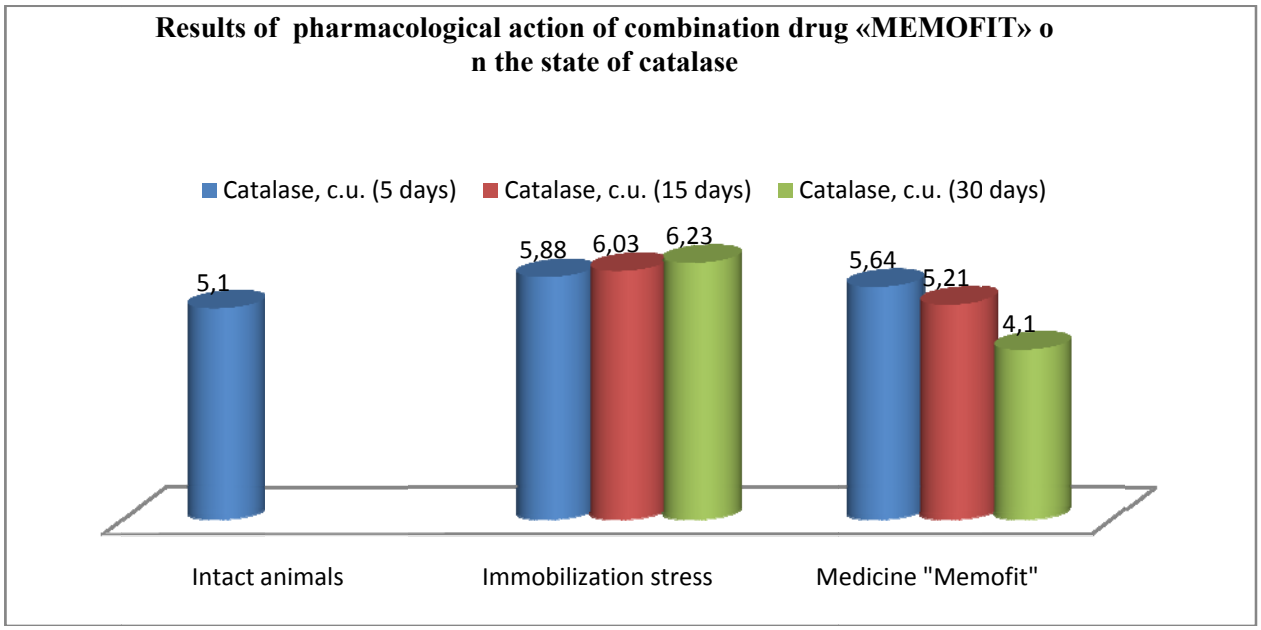

Figure 4

norm, and SOD parameters reach 6.98 ± 0.23 c.u. that is twice as much as the control. The level of catalase on the 30-th day reaches 6.23 ± 0.03 c.u. that is twice as much as the norm, SOD reaches 7.13 ±0.89 c.u. that is two and a half times bigger than the control.

Figures 3 and 4 show that on the 5-th day the tested combination drug "Memofit" influences the level of catalase and SOD in the blood serum of the tested rats statistically significant and these parameters decrease in relation to immobilization stress. Thus, SOD level at immobilization stress + combination drug "Memofit" is 5.44 ± 0.13 c.u. respectively, that is statistically significant in relation to immobilization stress 6.93 ± 0.19 c.u. ($P<0.05$). The level of catalase at immobilization stress + combination drug "Memofit" reaches 5.64 ± 0.12 c.u., that is in 1.04 times less in comparison with this parameter for the group of animals that were subjected to immobilization stress 5.88 ± 0.26 c.u., but do not reach this parameter for the control group of animals.

The combination drug "Memofit" on the 15-th day decreases the level of catalase and SOD statistically significant in relation to immobilization stress and control. Thus, the level of catalase at immobilization stress + combined medicine "Memofit" reaches 5.21 ± 0.34 c.u. that is statistically significant in relation to the group of animals, that were subjected to immobilization stress 6.03 ± 0.21 c.u. ($P<0.05$). The level of SOD at immobilization stress + combination drug "Memofit" is 4.52 ± 0.11 c.u., respectively, that is statistically significant in relation to immobilization stress 6.98 ± 0.23 c.u. and control 3.59 ± 0.11 c.u. ($P<0.05$).

The tested combination drug "Memofit" on the 30-th day reduces the level of catalase and SOD statistically significant in relation to the group of rats that were subjected to immobilization stress. Thus, the level of catalase at immobilization stress + combination drug "Memofit" is 4.12 ± 0.09 c.u., correspondently, that is statistically significant in relation to the group of animals that were subjected to immobilization stress 6.23 ± 0.03 c.u. ($P<0.05$). The level of SOD at immobilization stress + combination drug "Memofit" reaches 4.16 ± 0.09 c.u. correspondently, that is statistically significantly in relation to immobilization stress 7.13 ± 0.89 c.u. and control 3.59 ± 0.11 ($P<0.05$).

Conclusions. Taking into consideration the results of POL parameters (DC and NBA-AP) at immobilization stress, we can make a conclusion that these parameters on the 5-th and 15-th day do not correct statistically significant in relation to control, but correlate in relation to immobilization stress. It is only on the 30-th day, the combination drug "Memofit" reduces the level of DC and TBA – AP statistically significant in relation to immobilization stress and reaches to control.

Taking into account the research results of catalase and SOD under the conditions of chronic immobilization stress, we can make a conclusion that, these parameters are corrected better than LPO para-

meters (DC and TBA-AP), it gives evidence that the tested combination drug “Memofit” has significant antioxidant action.

Also, paying attention to behavioral reactions of rats during the experiment under the conditions of immobilization stress, we can make a conclusion that the combination drug “Memofit” has significant sedative effect.

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СОЗЫЛМАЛЫ ИММОБИЛИЗАЦИЯЛАУ ҚҰРАЛДАРЫНЫҢ ЖАҒДАЙЫНДА «МЕМОФИТ» АРАЛАС ҚҰРАЛДАРЫНЫҢ НЕЙРОТРАНСМИТТЕРЛІК ӘСЕРІН ЗЕРТТЕУ

Аннотация. Біріккен мемофит агентінің нейротрансмиттерлік әсері қорғасын тотығуының және антиоксиданттық жүйенің параметрлері бойынша, атап айтқанда: бастапқы тотығу өнімдері - диенді конъюгаттар мен қосалқы өнімдер - malonic aldehyde және каталаза және супероксидтік дисмутаза белсенділігі деңгейлері бойынша зерттелді. Эксперименттік зерттеу орташа массасы 210-230 г 18 Ваг егеуқұйрықтарында жүзеге асырылды, созылмалы нейромашалық шиеленістің үлгісі бойынша стресс-модифицирующий әсер зерттелді, ол 5,15,30 күн бойы ойнатылды. Иммобилизациондық стресс пластикалық торларда - сөрелерде егеуқұйрықтарды күнделікті күтумен 5 сағаттан модельденді. Зерттеу үшін сарысу пайдаланды. Спектрофотометриялық әдіспен бастапқы тотығу өнімдерінің деңгейі - диенді конъюгаттар (DC) және қосалқы өнімдер - malonic dialdehyde (MDA) және антиоксидант жүйесінің жағдайы анықталды. FLOOR негізінде, TBC-AP және DK индикаторларының 30 күндік кезеңде ғана комбинациялық препараттың зерттеуі, DK және TBA-AP статистикалық тұрғыдан иммобилизация стрессіне қатысты сенімділікпен төмендейді және оны басқаруды жақындастырады деген қорытындыға келуі мүмкін. Иммобилизациялық стресс жағдайында каталаза деңгейі + «Мемофит» есірткі 4,12±0,09 текше метрге дейін жетеді, тиісінше иммобилизация стрессіне ұшыраған жануарлар тобына қатысты, мүмкін, 6,23±0,03 куб. (P <0,05). Иммобилизациялық стресс жағдайында SOD деңгейі + «Мемофит» аралас препарат 4,16±0,09 текше метрді құрайды. тиісінше, 7.13±0.89 куб. Иммобилизациялық стрестке өте ұқсас және 3,59 ± 0,11 АҚШ доллары (P <0,05).

Е. В. Савельева[1], И. Н. Владимирова[2], О. В. Куликова[1], Т. С. Тишакова[1], Я. А. Бутко[2]

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ИЗУЧЕНИЕ НЕЙРОМЕДИАТОРНОГО ДЕЙСТВИЯ КОМБИНИРОВАННОГО СРЕДСТВА «МЕМОФИТ» В УСЛОВИЯХ ХРОНИЧЕСКОГО ИММОБИЛИЗАЦИОННОГО СТРЕССА

Аннотация. Нейромедиаторное действие комбинированного средства «Мемофит» было изучено с использованием параметров продуктов перекисного окисления лидидов и антиоксидантной системы, а именно: по уровню первичных продуктов окисления – диеновых конъюгатов и вторичных продуктов – малонового альдегида, и активности каталазы и супероксидисмутазы. Экспериментальное исследование было проведено на 18 крысах линии WAG средней массой 210–230 г. Моделирующее стресс действие изучали на модели хронического нервно-мышечного напряжения, которое воспроизводили на протяжении 5-ти, 15-ти, 30-ти суток. Иммобилизационный стресс моделировали путём ежедневного содержания крыс в течение 5 часов в пластиковых клетках - пеналах. Для исследования использовали сыворотку крови. Уровень первичных продуктов окисления – диеновых конъюгатов (ДК) и вторичных продуктов – малонового диальдегида (МДА) и состояние антиоксидантной системы определяли спектрофотометрическим методом. На основании ПОЛ можно сделать вывод, что показатели ТБК-АП и ДК только на этапе 30-ти суток исследуемый комбинированный препарат понижает уровень ДК и ТБК-АП статистически вероятно достоверно относительно иммобилизационного стресса и приближает к контролю. Уровень каталазы в условиях иммобилизационного стресса + комбинированный препарат «Мемофит» достигает 4,12±0,09 у.е., соответственно, то вероятно достоверно относительно группы животных, которых подвергали иммобилизационному стрессу, 6,23±0,03 у.е. (P<0,05). Уровень СОД в условиях иммобилизационного стресса + комбинированный препарат «Мемофит» достигает 4,16±0,09 у.е. соответственно, що вероятно достовірно относительно иммобилизационного стресса 7,13±0,89 у.е. и контроля 3,59±0,11 у.е. (P<0,05).

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