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ANTIHYPOXIC ACTIVITY OF GETASANE POLYPHENOLS IN EXPERIMENTAL HEMIC HYPOXIA

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Abstract In this article, we studied the antihypoxic activity of the polyphenol hetasan on an experimental model of hemic hypoxia. Studies have shown that the compounds of hetasan have antihypoxic activity and are more effective in medical practice than quercetin and mexidol. In the future, these polyphenols can be used in the development of drugs used for the prevention and treatment of respiratory dysfunction, heart failure, circulatory disorders and other pathological conditions.
Keywords antihypoxic, hetasan, polyphenol, hypoxia, $NaNO_2$

Introduction: Hypoxia is a pathological process, an absolute or relative lack of the level of biological oxidation and energy supply in various tissues of the body. Currently, modern medical and biological research has shown that hypoxia is the main factor in the development of the pathogenesis of various diseases, regardless of the etiology of its origin. The effect of hypoxia is observed in ischemic heart disease, impaired blood circulation and respiration, the immune system, in neurodegenerative diseases and in the pathogenesis of the development of other diseases. Pharmacological correction of physiological and metabolic disorders with antihypoxic drugs is one of the urgent problems of public health, pharmaceuticals and modern biology.
In the leading research centers of the world, scientific research is being intensively carried out to study the mechanisms of action of plant polyphenols on the human body and animals. As a result of research, it has been shown that polyphenols have a therapeutic effect on the body in various pathologies and have their antioxidant, mebranoactive and antihypoxant properties. Scientific research on the identification of new antihypoxant drugs requires studying the mechanisms of action of polyphenolic compounds on the body under hypoxic conditions.
Materials and methods: In in vivo experiments, a model of experimental hypoxia was formed and methods for the detection of antihypoxic substances were described. At the same time, to form models of normobaric and hemic hypoxia in laboratory mice, experimental animals were divided into four groups: I - control group (hypoxia + saline solution), II - experimental group (hypoxia + "Mexidol"), III - experimental group (hypoxia + quercetin), IV - experimental research group (hypoxia + hetasan). The number of animals in each group is 5 heads. Experiments on hemic hypoxia with $NaNO_2$ were carried out using two types of doses, a lethal dose of 150 mg/kg of body weight and an absolute lethal dose of 200 mg/kg of body weight. In studies to search for new antihypoxic substances, the physiological criteria of animals in the control and experimental groups were taken into account, that is, the period of residence and indicators of its duration. Polyphenol hetasan belongs to the 5th class of non-toxic compounds, their toxicity level LD_{50} is 4800 mg/kg.
Resultats and discussion: Hypoxia is a pathological process, an absolute or relative lack of the level of biological oxidation and energy supply in various tissues of the body. In experimental studies, hemic hypoxia is a convenient screening model for identifying new antihypoxic agents. A decrease in the amount of O_2 in the blood directly causes a deficiency of O_2 in tissues and cells, and leads to the development of a hemic form of hypoxia in the body. In research experiments, the antihypoxic activity of hetasan was studied on a model of hemic hypoxia. When forming this model of hypoxia, we used sodium nitrite salts ($NaNO_2$). In experimental experiments, doses of $NaNO_2$ salt of 150 and 250 mg/kg were used. Since a dose of 150 mg/kg NaNO2 forms a moderate manifestation of hemic hypoxia in the body, a dose of 250 mg/kg leads to the development of a severe form of hemic hypoxia. In studies, the antihypoxic activity of hetasan was studied at a dose of $NaNO_2$ of 150 mg/kg (Fig. 1).

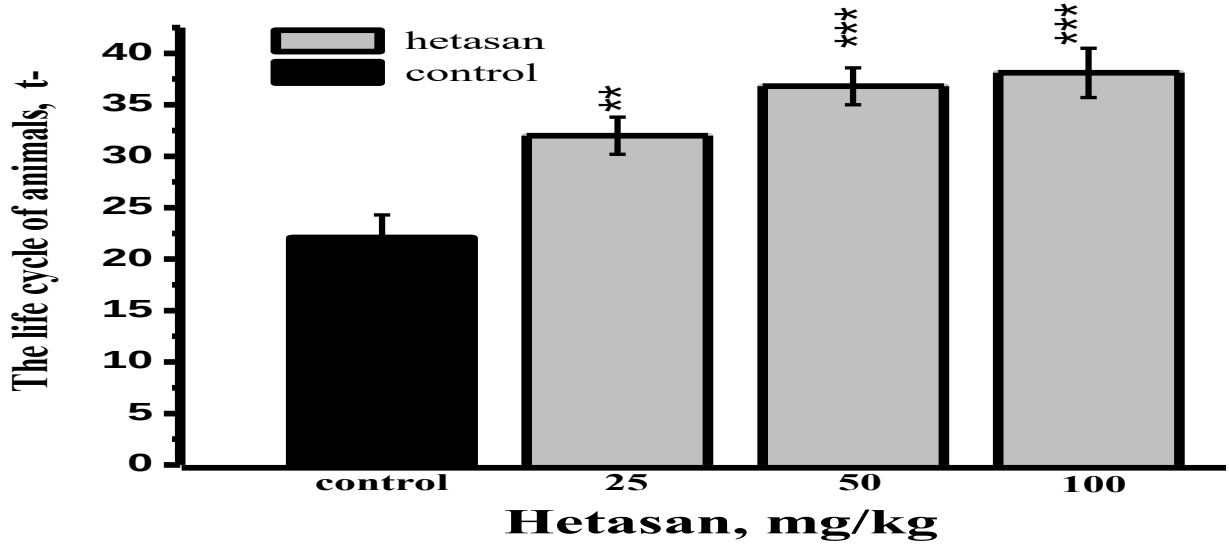

Fig. 1. Antihypoxic activity and efficacy of different doses of hetasan

Note: On the ordinate axis - the life expectancy of experimental animals is expressed in t-minutes, on the abscissa axis - ruthenium doses. ** P<0.01; *** P<0.001; n = 5.

The following studies were carried out to determine the antihypoxic activity of hetasan in a model of hemic hypoxia. For this, doses of hetasan were selected (25 mg/kg of body weight; 50 mg/kg and 100 mg/kg), since this drug is a low-toxic substance of class IV, and its activity was studied under the influence of these doses. The experimental results showed that in all studied doses, hetasan exhibited antihypoxic properties. In particular, in the experiments, the life expectancy of animals in the control group was 22.1±2.2 minutes. The survival time of animals under hypoxic conditions was 32.0±1.8 minutes at a dose of 25 mg/kg of hetasan polyphenol, while hetasan increased the survival of animals by 9.9 minutes, and its antihypoxic efficacy was 44.7%. A similar activity was observed at doses of 50 mg /kg and 100 mg/kg hetasan, respectively (36.8±1.8 minutes and 38.1±2.4 minutes). At these doses, the survival rate of the animals increased by 14.7 and 16.0 minutes. Statistical analysis of the results showed that the difference between the activity of hetasan at doses of 50 and 100 mg/kg was relatively low. Under these conditions, the antihypoxic efficacy of hetasan was 66.5% and 72.3%, respectively. On this basis, when determining the antihypoxic efficacy of hetasan and other polyphenols, a dose of 50 mg/kg of body weight was chosen in mice (Fig 1.).

When assessing the effectiveness of antihypoxic and other drugs, it is recommended to compare their activities with widely used drugs in pharmacology. In this regard, in this work, the antihypoxic properties of hetasan are compared with quercetin and Mexidol. According to the literature, quercetin, along with antioxidant, antiradical and membrane-active properties, has an antihypoxic effect, and Mexidol is now widely used in medical practice as an antihypoxic drug. In subsequent experiments, in order to assess the antihypoxic efficacy of hetasan, its activity was studied in comparison with quercetin and Mexidol.

At the same time, the life expectancy of animals of the I control group averaged 26.2 ± 2.56 minutes. It should be noted that between 25 - 28 minutes of the duration of the experiment, mortality was observed in all animals of the control group and amounted to 100% (table.1.). Under the action of hetasan 50 mg/kg with intoxication of the body with $NaNO_2$ at a dose of 150 mg/kg, the average life span of the animals was 46.5±1.11 minutes. Hetasan increased the survival rate of animals by 20.3 minutes compared to the control group. Under these conditions, the antihypoxic activity of hetasan was 76.7% higher than in the control animals (Fig. 2.).

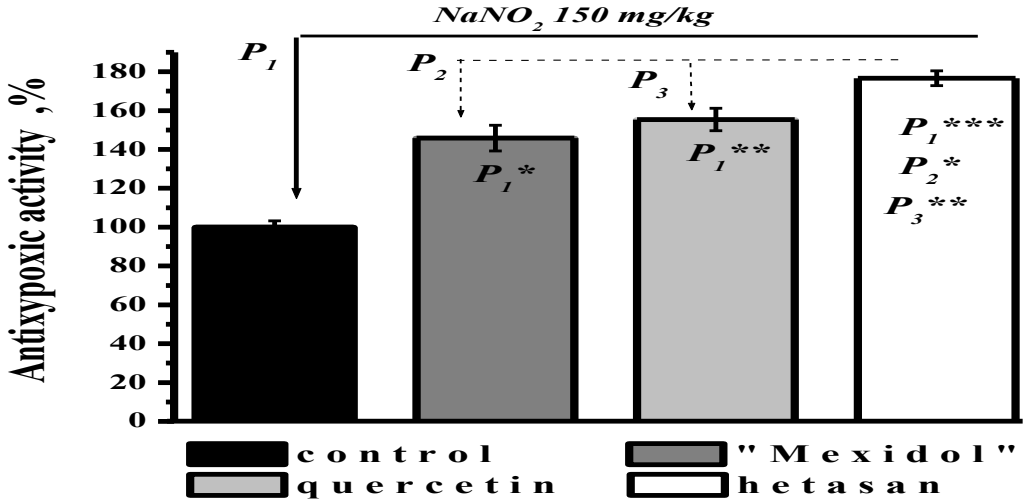

Fig. 1.Antihypoxic activity of hetasan in a model of hemic hypoxia.

Note: on the ordinate - the antihypoxic activity of the test substances is presented in%, on the abscissa - the experimental groups. P_1 - ratio of experimental groups with control, P_2 - ratio of investigated substances with "Mexidol" and P_3 - ratio of investigated substances with quercetin. *P <0.05; ** P <0.01; *** P <0.001; n = 5.

Effect of hetasan on the life cycle of animals in the model of hemic hypoxia at a dose of 150/mg of $NaNO_2$

xperimental groups Animals living	**mals living period, minutes**	**increase in duration, minutes**
Control	26.2±2.56	-
Hypoxia + Mexidol	38,2±1,01	12,0
Hypoxia quercetin	40,2±1,14**	14,0
Hypoxia + hetasan	46,5±1,11***	20,3

Note: The increase in life expectancy of the study animals was calculated in minutes relative to the life expectancy of the control group animals of the experimental groups. ** P <0.01; *** P <0.001; n = 5.

In conclusion, we can say that a dose of $NaNO_2$ of 150 mg / kg leads to the development of a moderate form of hemic hypoxia in experimental mice. According to studies, an average of 30% of animals poisoned with hetasan and quercetin $NaNO_2$ survived. These data are consistent with the results of studies on the antihypoxic activity of hatasan polyphenol based on the normobaric hypoxia model. Consequently, hetasan exhibit high antihypoxant activity in moderate hypoxia.These results are of interest from the point of view of studying the antihypoxic activity of the test substances against the background of the action of a dose of $NaNO_2$ at 250 mg/kg (absolute mortality). The literature describes that a dose of 250 mg/kg $NaNO_2$ causes severe forms of hypoxia in the body. At a dose of 250 mg/kg $NaNO_2$, the lifespan of animals treated with hetasan was 13.08 minutes (tabl.2.). The fact that the survival period of animals under the influence of hetasan was 20.2 minutes indicates an increase in the antihypoxic activity of hetasan by 46.3% compared to the control (Fig. 3). With this form of hypoxia in the presence of quercetin and mexidol, the following was observed: the survival rate of animals taking quercetin increased by 5.0 minutes compared to the control group and showed 36.2% antihypoxic activity (Fig. 3). Under the influence of "Mexidol" it was found that the survival rate of the animals increased by 4.2 minutes in comparison with the control group, i.e. antihypoxic activity increased by 30.4%. However, in experiments, the survival rate of animals with this form of hemic hypoxia was not preserved. That is, in our experiments at the end of the experiment, in this case, all the animals in the group died.

Effect of hetasan on the life cycle of animals in the model of hemic hypoxia at a dose of 250/mg of $NaNO_2$

xperimental groups animals living	nimals living period, minutes	I increase in duration, minutes
Control	13,8±1,06	-
Hypoxia + Mexidol	18,0±1,01	4,2
Hypoxia quercetin	18,8±1,09*	5,0
Hypoxia + hetasan	20,2±1,16**	6,4

Note: The increase in life expectancy of the study animals was calculated in minutes relative to the life expectancy of the control group animals of the experimental groups. ** P <0.01; *** P <0.001; n = 5.

Thus, in the experiments, the polyphenol hetasan retained antihypoxant activity even at a dose of 250 mg/kg. At the end of the experiments, the antihypoxic activity of the studied polyphenols (hetasan) was compared with the life cycle of experimental animals, taking into account the survival rate.

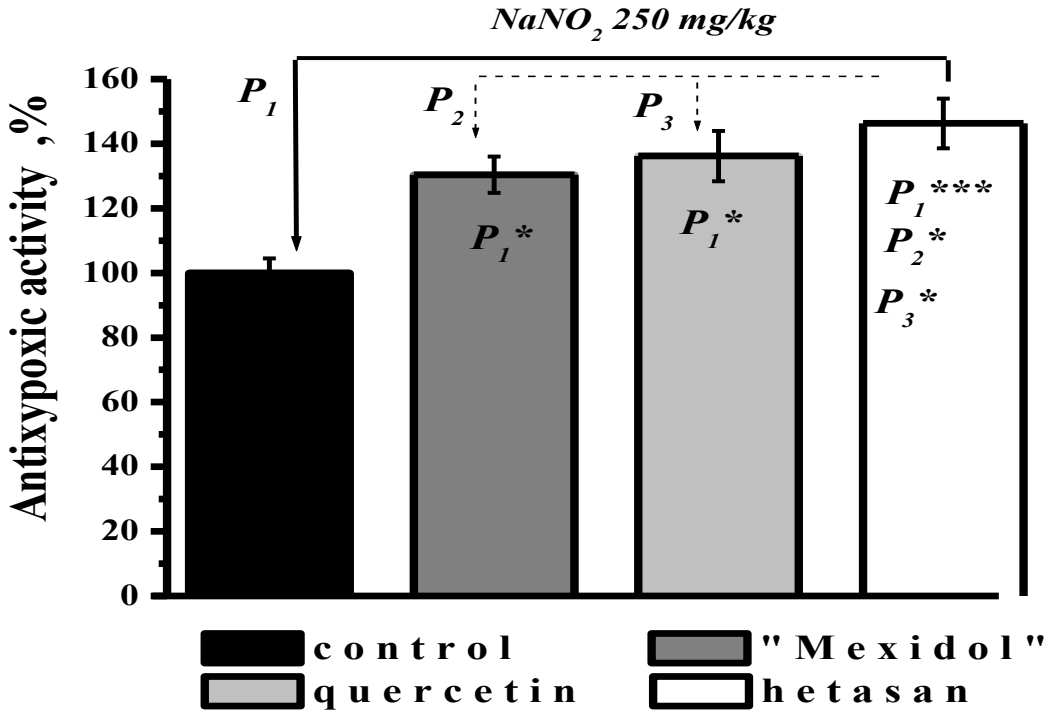

Fig. 3.Antihypoxic activity of hetasan in a model of hemic hypoxia.

Note: on the ordinate - the antihypoxic activity of the test substances is presented in%, on the abscissa - the experimental groups. P_1 - ratio of experimental groups with control, P_2 - ratio of investigated substances with "Mexidol" and P_3 - ratio of investigated substances with quercetin. *P <0.05; ** P <0.01; *** P <0.001; n = 5.

At a $NaNO_2$ dose of 250 mg/kg, 100% mortality was observed in all animals of the experimental group within 10–18 minutes of the duration of the experiment (with an average difference of 8 minutes). Therefore, the toxic effect of the 250 mg/kg dose ($NaNO_2$) received indicates that it was highly toxic compared to the 150 mg/kg dose. This process also strongly influenced the physiological state of animals, reducing their survival rate. At a dose of 250 mg / kg $NaNO_2$, the survival time of animals in the control group was 13.8±1.06 minutes. These values differed by about 12.4 minutes with moderate hemic hypoxia compared

to the effect of $NaNO_2$ at a dose of 150 mg/kg. In models of hemic hypoxia (moderate to severe), the polyphenol hetasan exhibited high antihypoxic properties. Their antihypoxic effect is more active than that of quercetin and Mexidol, which will become the basis for the development of new promising antihypoxic drugs.

CONCLUSION. It was found that with an average form of hemic hypoxia, hetasan increase the lifespan of animals in the experimental group by 6.4-20.3 minutes, compared with the control group, while the antihypoxic efficacy is from 46.3% to 76.7% . Thus, the data obtained show that the compounds under study have powerful antihypoxic properties. The antihypoxic activity of the compounds of hetasan in experimental models of hypoxia turned out to be more effective than that of quercetin and Mexidol, which is used in medical practice. In the future, these polyphenolic compounds can be used in the development of drugs used for the prevention and treatment of respiratory dysfunction, heart failure, circulatory disorders and other pathological conditions.

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