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Study of Anti-Inflammatory Activity "Dorusim"

Khakimov Z. Z.[1], Rakhmanov A. Kh.[1,*], Babazhanov A. U.[2], Tursunova L. I.[3], Khadzhieva U. A.[3]

[1]Tashkent Medical Academy, Tashkent, Uzbekistan
[2]Urgench Branch of the Tashkent Medical Academy, Tashkent, Uzbekistan
[3]Uzbek Research Chemical and Pharmaceutical Institute named after. A. Sultanov, Tashkent, Uzbekistan

Abstract The results of experimental studies conducted on adult white male rats showed that the phytocomposition Dorusim has a pronounced anti-exudative activity in aseptic arthritis induced by various phlogogens. An effective anti-inflammatory dose of Dorusim in enteral administration is 50 mg/kg. A possible mechanism of the anti-inflammatory activity of Dorusim is its suppression of the release of histamine from mast cells and the synthesis of prostaglandins.

Keywords Aseptic arthritis, Phytocomposition, Medicinal plants, Antiinflammatory agents

1. Introduction

Recently, the problem of drug safety has become increasingly relevant worldwide due to the fact that mortality caused by adverse reactions ranks 5th globally, following diseases of the cardiovascular system, lungs, oncological pathologies, and injuries [1]. Modern medicine has a wide arsenal of anti-inflammatory drugs, but their regular use leads to the development of a number of side effects such as gastro-, nephro-, cardio-, hemato-, hepatotoxicity, which is associated with their ability to penetrate through histohematic barriers and the manifestation of systemic action [2,3,4,5,6,7,8]. Therefore, the search for new compounds with anti-inflammatory action is an urgent task of pharmacology. In recent years, interest in medicinal plants has increased significantly due to the fact that the use of synthetic drugs is accompanied by various side effects, and on the other hand, a high content of biologically active substances in the complex. Literature data indicate that medicinal plants: *Herba alhagi, Folium Uvae ursi, Fructus Rosae, Glycyrrhiza glabra* and *Flores chamomillae* have antioxidant and membrane stabilizing effects [9,10,11,12], which allows us to assume that this phytocomplex has an anti-inflammatory effect. The literature data show that this phytocomposition has not been specifically studied as an anti-inflammatory agent.

The purpose of this work was to study the anti-inflammatory activity of Dorusim.

2. Material and Methods

* Corresponding author:
dr.ali.fl@mail.ru (Rakhmanov A. Kh.)
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2.1. Experiments

Experimental studies were carried out on adult white male rats weighing 145-160 g, obtained from the vivarium of the Department of Sanitary and Epidemiological Surveillance of the Main Medical Department under the Administration of the President of the Republic of Uzbekistan. Prior to the start of the experiment, all animals were examined, weighed after a two-week quarantine. Age, sex, physical activity and skin condition of animals were taken into account. Each experimental and control group consisted of six individuals. During experimental studies, laboratory animals were kept in a vivarium in plastic cages, bedding of sawdust at a temperature of 20-24℃, in a well-ventilated room and day/night light regimen. Humidity was at least 50%. Feeding of animal was calculated according to their age. For the study, we selected extracts of the following medicinal plants *Herba alhagi, Folium Uvae ursi, Fructus Rosae, Glycyrrhiza glabra* and *Flores chamomillae*, and it was conditionally named "Dorusim". Diclofenac sodium (Belmedpreparaty) and Canephron (Bionorica SE., Germany), which is a mixture of dry extracts of medicinal plants, were used as a reference drugs. The classical models of experimental aseptic arthritis induced by a formalin (2%), carrageenan (1%), dextran (6%) and histamine (0,1%) were used to study the anti-exudative activity of the above compositions of dry extracts of medicinal plants [13,14,15,16]. The phlogogen solutions were injected (0.1 ml per animal) subplantarly (under the plantar aponeurosis) into the hind right paw of rats. [13]. The volume of paws of rats before the injection of the phlogogen was considered initial and was taken as 100%. One day and 1 hour before the induction of aseptic arthritis, rats of the control group were administered intragastrically an equivolume amount of water as well as animals of the experimental groups were administered the Dorusim in various doses of 25, 50 and 100 mg/kg, canefron - 100 mg/kg and sodium diclofenac - 10 mg/kg. The volume of the paws

of the animals was measured by the oncometric method using a plethysmometer (Ugo Basile Srl, Italy) before and after the injection of phlogogens. The anti-inflammatory activity of the studied compounds was judged by the difference in paw volume before the start of the experiments and at the moment of maximum development of edema. The value of anti-inflammatory activity (AIA) of the preparations was calculated according to the formula (5):

$$AIA = Vcon – Vexp / Vcon \times 100 = \%$$

where; V con - average increase in paw volume in control group, cm3, Vexp –average increase in paw volume in experimental group, cm3.

2.2. Statistical Analysis

The data obtained were processed by the method of variation statistics using the paired Student's test and one-way analysis of variance using the standard software package BIOSTAT 2009 with an assessment of the significance of indicators (Mean±Std error). Differences in the compared groups were considered significant at a significance level of 95% $p < 0.05$.

3. Results and Discussion

According to the requirements of preclinical studies for new compounds with anti-exudative action, it is necessary to conduct tests on various models of aseptic arthritis induced by various phlogogens [17].

The phlogogenic effect of formalin, as is known, is due to its interaction with the amino groups of proteins and the release of biogenic amines and free amino acids, followed by a disturbance of isoionia and isotonia at the injection site [13,18,19] Analysis of the results of the studies conducted on this model showed that 2, 4 and 6 hours after the phlogogen injection a distinct aseptic arthritis developed under the influence of formalin, which manifested in an increase in the volume of the paws of rats by 72.8; 114.4 and 101.4%, respectively. At the same time, the noted effect with slight fluctuations (increase by 90.0 and 74.3%) persists after 1 and 2 days from the start of the experiment. As can be seen from the data in Table 1, the preliminary administration of diclofenac sodium inhibits the development of paw edema 2, 4, 6, 24 and 48 hours after injection of formalin compared with the control group by 20.4; 29.1; 32.2; 37.6 and 41.2%, respectively.

In the indicated periods of observation, AIA was 27.4; 25.9; 38.0; 42.8 and 46.1% respectively. There was also a clear suppression of the development of paw edema in the group of animals that received Dorusim preventively. At the same time, the AIA of Dorusim was 23.5; 33.3 and 35.2% after 2, 4 and 6 hours, as well as 40.0 and 42.3% after 1 and 2 days of the experiment. It can be seen that the pharmacological activity of Dorusim is not significantly inferior to diclofenac sodium. In our experiments, the animals previously treated with canefron showed the least anti-exudative effect.

Table 1. Influence of Dorusim, canefron and diclofenac sodium on the course of aseptic arthritis induced by formalin (M±m, n=6)

Groups	Study time, hours (paw volume, cm^3)					
	initial	2 hours	4 hours	6 hours	8 hours	24 hours
Control	0,70 ± 0,03	1,21 ± 0,09* 0,51 ± 0,04	1,48 ± 0,14* 0,78 ± 0,07	1,41 ± 0,13* 0,71 ± 0,07	1,33 ± 0,13* 0,63 ± 0,05	1,22 ± 0,11* 0,52 ± 0,04
Canefron, 100 мг/кг	0,66 ± 0,02	1,11 ± 0,10* 0,45 ± 0,04	1,30 ± 0,12* 0,64 ± 0,05	1,22 ± 0,11* 0,56 ± 0,05	1,14 ± 0,09* 0,48 ± 0,04#	1,05 ± 0,08 0,39 ± 0,03#
Dorusim, 50 мг/кг	0,75 ± 0,04	1,14 ± 0,14* 0,39 ± 0,04#	1,27 ± 0,14* 0,52 ± 0,04#	1,21 ± 0,15* 0,46 ± 0,04#	1,13 ± 0,13* 0,38 ± 0,04#	1,05 ± 0,13 0,30 ± 0,03#
Diclofenac, 10 мг/кг	0,64 ± 0,02	1,01 ± 0,11* 0,37 ± 0,04#	1,14 ± 0,13* 0,50 ± 0,05#	1,08 ± 0,13* 0,44 ± 0,04#	1,00 ± 0,12* 0,36 ± 0,04#	0,92 ± 0,11 0,28 ± 0,03#

Note: *Here and in other tables in the numerator are the absolute indicators of the volume of the paws, and in the denominator the difference in edema of the paws compared to the initial volume;* ******* *- significant difference comparing with the initial indicators of corresponding groups of animals, #-significant difference compared to the control group at the corresponding hours of study.*

The AIA of canefron ranged from 11.8 to 25.0% during the observed periods. Consequently, on the model of formalin inflammation, Dorusim showed a pronounced anti-inflammatory effect and surpassed the phyto-drug canefron in its activity and its activity was not noticeably inferior to diclofenac sodium. It should be noted that the AIA of medicines, especially Dorusim as diclofenac sodium rose with an increase in the period of observation.

The models of carrageenan and formalin paw edema in laboratory animals complement each other, but they are not interchangeable as models of inflammation. Therefore, it is important to use them correctly [13,20]. Experiments carried out in this aspect have shown that the studied medicines have an inhibitory effect on the development of carrageenan-induced aseptic edema of the paws of rats (Table 2). Thus, due to the influence of Dorusim, the volume of the paws of rats decreased by 31.2%, 40.4%, 43.7%, and 65.2% respectively compared to the control group after 2, 4, 6, and 24 hours from the start of the phlogogen injection. We observed a similar effect in animals that had previously been treated with diclofenac sodium, where the suppression of exudation development during the indicated observation periods was 33.3%, 42.6%, 45.0%, and 72.0%, respectively. It can be seen that the effect of Dorusim does not differ

significantly from that of diclofenac sodium. At the same time, the AIA of diclofenac was 33.3%, 42.6%, 45.0%, and 72.0% in the studied periods of observation, while the AIA of Dorusim was 28.6%, 38.2%, 41.7%, and 64.0%. Table 2 shows that Canefron weakly suppressed the intensity of paw edema development in rats (from 1.2% to 13.6%). It is known that the development of edema after the injection of carrageenan occurs in two phases. In the first hours of carrageenan inflammation, it is related to the action of kinins, while in later periods (after three and four hours), it is related to prostaglandins [13,21]. Based on this, it can be assumed that Dorusim, like sodium diclofenac, affects both phases of carrageenan inflammation. However, we noted a somewhat higher effect on the second - prostaglandin phase of inflammation.

Table 2. Influence of Dorusim, canefron and diclofenac sodium on the course of aseptic arthritis induced by carrageenan (M±m, n=6)

Groups	Study time, hours (paw volume, cm^3)				
	Initial	2	4	6	24
Control	0,55 ± 0,02	0,97 ± 0,06* 0,42 ± 0,06	1,23 ± 0,06* 0,68 ± 0,05	1,15 ± 0,05* 0,60 ± 0,05	0,80 ± 0,07* 0,25 ± 0,06
Canefron, 100 мг/кг	0,53 ± 0,03	0,93 ± 0,06* 0,40 ± 0,08	1,15 ± 0,05* 0,62 ± 0,07	1,03 ± 0,08* 0,50 ± 0,09	0,69 ±0,07 0,16 ± 0,07
Dorusim, 50 мг/кг	0,57 ± 0,01	0,87 ± 0,07* 0,30 ± 0,08	0,99 ± 0,07* 0,42 ± 0,07#	0,95 ± 0,07* 0,35 ± 0,07#	0,66 ± 0,04 0,09 ± 0,04#
Diclofenac, 10 мг/кг	0,55 ± 0,02	0,83 ± 0,04* 0,28 ± 0,04	0,94 ± 0,06* 0,39 ± 0,05#	0,88 ± 0,06* 0,33 ± 0,05#	0,62 ± 0,05 0,07 ± 0,04#

Note: *Here and in other tables in the numerator are the absolute indicators of the volume of the paws, and in the denominator the difference in edema of the paws compared to the initial volume;* ******* *- significant difference comparing with the initial indicators of the corresponding groups of animals,* ***#*** *- significant difference compared to the control group at the corresponding hours of study.*

Table 3. Influence of Dorusim, canefron and diclofenac sodium on the course of aseptic arthritis induced by dextran (M±m, n=6)

Groups	Dose, mg/kg	Study time, hours (paw volume, cm^3)				
		Initial	1 hour	2 hour	3 hour	4 hour
Control	-	0,68 ± 0,02	1,81 ± 0,06* 1,13 ± 0,04	1,71 ± 0,06* 1,03 ± 0,05	1,63 ± 0,06* 0,95 ± 0,04	1,56 ± 0,04* 0,88 ± 0,04
Dorusim	25	0,70 ± 0,02	1,54 ± 0,09* 0,84 ± 0,09#	1,45 ± 0,07* 0,75 ± 0,08#	1,35 ± 0,06* 0,65 ± 0,07#	1,28 ± 0,06* 0,58 ± 0,07#
Dorusim	50	0,69 ± 0,04	1,40 ± 0,09* 0,71 ± 0,07#	1,29 ± 0,09* 0,60 ± 0,06#	1,22 ± 0,09* 0,53 ± 0,07#	1,17 ± 0,09* 0,48 ± 0,07#
Dorusim	100	0,74±0,03	1,51 ± 0,04* 0,77 ± 0,04#	1,41 ± 0,04* 0,67 ± 0,04#	1,35 ± 0,04* 0,61 ± 0,04#	1,29 ± 0,04* 0,55 ± 0,04#
canefron	100	0,64 ± 0,04	1,45 ± 0,08* 0,81 ± 0,06#	1,37 ± 0,09* 0,73 ± 0,06#	1,33 ± 0,08* 0,69 ± 0,05#	1,25 ± 0,09* 0,61 ± 0,04#
diclofenac sodium	10	0,71 ± 0,04	1,39 ± 0,11* 0,68 ± 0,11#	1,30 ± 0,11* 0,59 ± 0,09#	1,23 ± 0,11* 0,52 ± 0,09#	1,17 ± 0,10* 0,46 ± 0,09#

Note: *Here and in other tables in the numerator are the absolute indicators of the volume of the paws, and in the denominator the difference in edema of the paws compared to the initial volume;* ******* *- significant difference comparing with the initial indicators of the corresponding groups of animals,* ***#*** *- significant difference compared to the control group at the corresponding hours of study.*

Table 4. The effect of Dorusim, canefron and diclofenac sodium on the course of histamine-induced aseptic arthritis (M±m, n=6)

Groups	Study time, hours (paw volume, cm^3)				
	Initial	30	60	120	180
Control	0,66 ± 0,04	1,77 ± 0,07* 1,11 ± 0,05	1,71 ± 0,05* 1,05 ± 0,03	1,62 ± 0,05* 0,96 ± 0,03	1,53 ± 0,06* 0,87 ± 0,04
Canefron, 100 mg/kg	0,76 ± 0,03	1,66 ± 0,10* 0,90 ± 0,08	1,60 ± 0,09* 0,84 ± 0,08#	1,50 ± 0,08* 0,74 ± 0,07#	1,42 ± 0,07* 0,66 ± 0,06#
Dorusim, 100 mg/kg	0,69 ± 0,04	1,42 ± 0,08* 0,73 ± 0,06#	1,34± 0,08* 0,65 ± 0,07#	1,27 ± 0,08* 0,58 ± 0,07#	1,18 ± 0,08* 0,49 ± 0,08#
Diclofenac 100 mg/kg	0,73 ± 0,04	1,48 ± 0,08* 0,75 ± 0,06#	1,41 ± 0,07* 0,68 ± 0,06#	1,33 ± 0,07* 0,60 ± 0,06#	1,25 ± 0,07* 0,52 ± 0,08#

Note: *Here and in other tables in the numerator are the absolute indicators of the volume of the paws, and in the denominator the difference in edema of the paws compared to the initial volume;* ******* *- significant difference comparing with the initial indicators of the corresponding groups of animals,* ***#*** *- significant difference compared to the control group at the corresponding hours of study.*

According to many scientists, the release of histamine, serotonin, and other biologically active substances from mast cells is an important mechanism for the development of the exudative phase of inflammation. These substances increase the permeability of the vascular wall [22,23,24,25].

In this regard, dextran is widely used as a phlogogenic agent to assess the anti-inflammatory activity of new potential drugs [13,25] because histamine and serotonin are one of the important inflammatory mediators. In addition, each medicine has its own range of pharmacological effects, so it is necessary to have information about the breadth of pharmacological activity to determine the effective dose. A separate series of experiments was carried out to resolve this issue and establish the effectiveness of Dorusim in the dextran model of inflammation.

The results of the latter study showed that injection of dextran resulted in an increase in the volume of rat's paw by more than 2.7 times after one hour, which remained almost unchanged until the end of the experiment (Table 3). In contrast, one hour after injection dextran in animals that had received Dorusim preventively at doses of 25 mg/kg, 50 mg/kg, and 100 mg/kg, the severity of edema decreased by 27.8%, 38.1%, and 37.4%, respectively. The AIA values from the indicated doses was 25.7; 37.2 and 31.8% respectively. It is noteworthy that the obtained results in subsequent follow-up periods were higher, especially from a dose of 50 mg/kg, under the influence of which the AIA values were 41.7% after 2 hours, 44.2% after 3 hours and 45.4% after 4 hours from the beginning of the experiment. Although, the medicine clearly suppressed the processes of exudation in other studied doses, but their AIA values were somewhat lower.

It should be noted that the data obtained suggests that the effective dose of Dorusim as an anti-inflammatory agent was 50 mg/kg. Table 3 indicates that one hour after the injection of the phlogogen, the AIA of diclofenac sodium and canefron was 39.8% and 28.3%, respectively. The analysis of the obtained results shows that, in terms of its pharmacological activity on the model of dextran-induced aseptic arthritis, Dorusim clearly surpasses Canefron and practically does not differ from the effect of diclofenac sodium. It is worth noting that the release of histamine, serotonin, and other biologically active substances from mast cells that impair the permeability of the vascular wall play a significant role in the mechanism of the phlogogenic action of dextran [13,22,23,24].

Histamine has a multidirectional effect on the human body, in particular, by stimulating H1 receptors located in the vessels, bronchi and stomach, causes an increase in vascular permeability, bronchospasm, lowering blood pressure, and increasing secretion of gastric juice [13,23,24,26]. Histamine is essentially detected simultaneously with the occurrence of damage in the focus of inflammation. It causes vasodilation of the microvasculature, increases their permeability, stimulates the pain nerve endings. Thus, histamine "starts" an acute inflammatory process. The appearance of histamine in the focus of inflammation is closely related to the degranulation of mast cells. The inflammatory process stimulates the synthesis of new mediators, the source of which are membrane lipids of activated mast cells and basophils, such as proteases, proteglycans, eosinophil chemataxis factors, kinins, complements, ecasonoids, leukotrienes, PAF and etc. [26]. Based on this, it seemed important to study Dorusim on the course of aseptic arthritis stimulated by histamine.

As shown by the results of this series of experiments, there was a pronounced increase in the processes of exudation, manifested by swelling of the paws of rats under the influence of histamine (table 4). So, in animals of the control group under the influence of histamine, the increase in the volume of the paws was 168.2% after 30 minutes, 159.1% after 60 minutes, 145.4% after 120 minutes, which remained with slight shifts until the end of the experiment. In contrast, 30 minutes after the injection of the phlogogen, the degree of edema was low compared to the control group by 37.1%, 38.9%, and 29.6% under the influence of dorusim, diclofenac sodium, and canefron, respectively. In subsequent observation periods, the observed effect increased, particularly in the group of animals that received Dorusim as a preventive measure. It is worth noting that Dorusim showed a certain superiority not only compared to Canefron but also to Diclofenac Sodium.

Thus, the new phytopreparation Dorusim has a significant AIA on various models of aseptic arthritis. At the same time, in terms of its pharmacological activity, it is somewhat superior to the phytopreparation canefron and is not inferior to the reference drug, diclofenac sodium. A possible mechanism for this effect of Dorusim is probably due to the suppression of free radical lipid oxidation, which is the source of the formation of arachidonic acid, and, accordingly, prostaglandins. In terms of proving this assumption, special additional studies are required.

4. Conclusions

1. The phytocomposition Dorusim has a pronounced anti-exudative activity in aseptic arthritis induced by various phlogogens.
2. The effective anti-inflammatory dose of Dorusim in enteral administration is 50 mg/kg.
3. In terms of its pharmacological activity, Dorusim is not inferior to sodium diclofenac and is noticeably superior to the phytopreparation Canefron.
4. A possible mechanism of the anti-inflammatory activity of Dorusim is its suppression of the release of histamine from mast cells and the synthesis of prostaglandins.

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REFERENCES

[1] Mitrofanova I. S., Stolbova M. V., Ovchinnikova Yu. G., Morina A. A., 2017, Adverse drug reactions, National Association of Scientists (NAU), 4, 31, 19-21.

[2] Mufazalova N.A., Valeeva L.A., R.A. Davletshin R.A., 2020, Undesirable drug reactions. Interaction of drugs. Part I. Non-steroidal anti-inflammatory drugs, Proc. allowance - Ufa: FGBOU VO BSMU of the Ministry of Health of Russia, 195 p.

[3] Prozzi R.G., Cañás M., Urtasun M.A., 2018, Riesgo cardiovascular de los anti-inflammatories no estereos, Medicana (Buenos Aires), 78, 349-355.

[4] Sriuttha R, Sirichanchuen B., Permsuwan U., 2018, Hepatotoxicity of Nonsteroidal Anti-Inflammatory Drugs: A Systematic Review of Randomized Controlled Trials, Hindawi International Journal of Hepatology, 13, https://doi.org/10.1155/2018/5253623.

[5] Kareva E.N., Oleinikova O.M., Serebrova S.Yu., 2022, Side effects of non-steroidal anti-inflammatory drugs and ways to prevent them, Experimental and Clinical Pharmacology, 85, 3, 33-44.

[6] Ying X. H., Bao D. N., Jiang H. Y., Shi Y. D., 2022, Maternal non-steroidal anti-inflammatory drug exposure during pregnancy and risk of miscarriage: a systematic review and meta-analysis, European Journal of Clinical Pharmacology, 78, 2, 171-180.

[7] Gunaydin, C.. Bilge S., 2018, Effects of nonsteroidal anti-inflammatory drugs at the molecular level, The Eurasian Journal of Medicine, 50, 2, 116-121.

[8] Wongrakpanich S., Wongrakpanich A., Melhado K., Rangaswami J., 2018, A comprehensive review of non-steroidal antiinflammatory drug use in the elderly, Aging and Disease, 9, 1, 143-150.

[9] Aleksashina S.A., Makarova N.V., Demenina L.G. 2019, Antioxidant potential of rose hips, Nutritional Issues, 88, 3, 84–89.

[10] Khasanova S.R., 2016, Experimental and theoretical substantiation of the creation and standardization of medicinal herbal preparations with antioxidant activity, Abstract of the dissertation for the degree of Doctor of Pharmaceutical Sciences, 46 p.

[11] Ryazanova T.K., 2022, Theoretical and experimental substantiation of approaches to the standardization of medicinal herbal raw materials and medicinal herbal preparations containing biologically active substances of aromatic and terpenoid nature, Abstract of the dissertation for the degree of Doctor of Pharmaceutical Sciences, 45 p.

[12] Danatarov B. G., Gurbangeldiev B. D., 2022, An innovative method for obtaining a dry extract of camel thorn, Young scientist, 3, 398, 1-4.

[13] Khakimov Z.Z., Rakhmanov A.Kh., Mavlanov Sh.R., 2022, Anti-inflammatory activity of a mixture of medicinal plants. LLC "TIBBIYOT NASHRIOTI MATBAA UYI", Tashkent, 228 p.

[14] Khakimov Z.Z., Rakhmanov A.Kh., Mavlanov Sh.R., 2018, Investigation of influence of medicinal collection containing flavonoids on the course of histamine induced inflammation, Scientific Journal “Fundamentalis Scientiam”, 21, 45-47.

[15] Khakimov Z. Z., Rakhmanov A. Kh., Khadzhieva U. A., Tursunova L.I., 2023, Antiexudative activity of a new phytocomposition consisting from the flora of Central Asia, American Journal of Medicine and Medical Sciences, 13, 2, 39-42.

[16] Khakimov Z. Z., Rakhmanov A. Kh. Mavlanov Sh.R., 2019, Study of the Influence of Dry Extract of Medicinal Plants on the Course of Carrageenan-Induced Inflammation, American Journal of Medicine and Medical Science, 9, 8, 307-310.

[17] Mironov A.N., 2012, Guidelines for conducting preclinical studies of drugs. Part one. -M. Grif and K, 944 p.

[18] Kong Kh. Kh., Khaziakhmetova V.N., Ziganshina L.E., 2015, Anti-inflammatory drugs, Experimental and Clinical Pharmacology, 78, 7, 24-31.

[19] Novikov V.E., Pozhilova E.V., Ilyukhin S.A., 2015, Effect of antihypoxants on the development of acute formalin edema, Reviews on Clinical Pharmacology and Drug Therapy, 13, 1, 41-44.

[20] Kong Kh.Kh., Sibgatulina R.R., Khabibrakhmanova A.M., 2017, The possibility of using cellular test systems for screening for anti-inflammatory activity of new 5(S)-mentyloxy derivatives of 2(5H)-furanone, Kazan Medical Journal, 98, 2, 211-217.

[21] Necas J., Bartosikova L., 2013, Carrageenan: a review, Veterinarni Medicina, 58, 4, 187-205.

[22] Pathophysiology. Under the editorship of Novitsky V.V., 2018, GEOTAR-MEDIA. Moscow, 896 p.

[23] Poryadina G.V., 2006, mediators of inflammation. Methodological developments for independent work of students of medical and pediatric faculties, 40 p.

[24] Poryadina G.V., 2006, Mediators of inflammation, Russian State Medical University. Toolkit. Moscow, 22 p.

[25] Schwartz G.Ya., Syubaev R.D., 2012, Guidelines for the preclinical study of non-steroidal anti-inflammatory drugs // Guidelines for conducting preclinical studies of drugs. Edited by Mironov A.N., Part one. - M.: Grif and K, 746-759.

[26] Tsirkin V.I., Khlybova S.V., 2006, The role of histamine in reproduction, Vyatka Medical Bulletin, 2, 1-12.