

10. Silkina YuV, Volkov KS, Shevchenko KV. Morfometrychna kharakterystyka rezystyvnoyi lanky hemomikrotsyrkulyatornoho rusla slynnnykh zaloz shchuriv pry khronichniy intoksykatsiyi etanolom. Morfolohiya. 2018; 12(1) :51–4. doi: 10.26641/1997-9665.2018.1.51-54. [in Ukrainian]
11. Spyrndonenko VV. Dobroyakisna hiperplaziya peredmikhurovoyi zalozy v praktytsi simeynoho likarya. Urolohiya. Nefrolohiya. Androlohiya [internet]. 2022; [tsytovano 2023 cherv.30];1–2 (26–27): 3–4. Dostupno: [https://health-ua.com/newspaper/tn\\_yro\\_nfro\\_andrologiya/69493-tematichnij-nomer-urologiya-nefrologiya-andrologiya--12-2627-2022-r](https://health-ua.com/newspaper/tn_yro_nfro_andrologiya/69493-tematichnij-nomer-urologiya-nefrologiya-andrologiya--12-2627-2022-r)
12. De Nunzio C, Salonia A, Gacci M, Ficarra V. Inflammation is a target of medical treatment for lower urinary tract symptoms associated with benign prostatic hyperplasia. World J Urol. 2020; 38(11) :2771–2779. <https://doi.org/10.1007/s00345-020-03106-1>.
13. Giovanni C, David ML; et al. "Age-Related Changes in General and Sexual Health in Middle-Aged and Older Men: Results from the European Male Ageing Study (EMAS)". Journal of Sexual Medicine - J SEX MED. 2010; 7(4) :1362–1380. doi: 10.1111/j.1743-6109.2009.01601.
14. Pronina OM, Koptyev MM, Bilash SM, Yeroshenko HA. Response of hemomicrocirculatory bed of internal organs on various external factors exposure based on the morphological research data. World of medicine and biology. 2018; 1(63) :153–7. doi 10.26.724 / 2079-8334-2018-1-63-153-157.

Стаття надійшла 22.07.2022 р.

DOI 10.26724/2079-8334-2023-3-85-224-229

UDC 615.322: 615.276

O.O. Nefodov, L.V. Eberle<sup>1</sup>, A.O. Tsisak<sup>1</sup>, O.I. Grisuk, O.I. Aleksandrova, O.M. Guzenko,  
A.M.I. Shkodovska, I.Y. Burega<sup>2</sup>  
<sup>1</sup>Odesa I.I. Mechnikov National University, Odesa  
<sup>2</sup>Odesa National Medical University, Odesa, <sup>3</sup>European Medical University, Dnipro

## EVALUATION OF ANTINOCICEPTIVE AND ANTIEXUDATIVE EFFECTS OF A COMPLEX HERBAL PREPARATION IN THE THERAPY OF SOMATIC PAIN AND INFLAMMATION OF DIFFERENT ORIGIN

e-mail: lidaeberle@gmail.com

Experimental studies of the antinociceptive effect of the complex herbal preparation on models of somatic pain induced by thermal and chemical stimuli were performed, and the antiexudative impact of the drug was established on models of inflammation of various genesis. The experimental sample of the herbal preparation is presented in the form of an ointment for transdermal administration and contains a complex of plant extracts: *Juglans nigra L.*, *Acorus calamus L.*, *Styphnolobium japonicum L.* and *Zingiber officinale L.* The study's results indicate the effectiveness of the drug in treating somatic pain with skin damage and in deep somatic manifestations of pain reactions. The activity of the herbal preparation was not inferior to that of the comparison drug. In the trypsin and zymosan models of edema, the complex herbal preparation has pronounced anti-inflammatory activity when administered transdermally. It suppresses cyclooxygenase and lipoxygenase activity, making it a promising object for further pharmacological study and introduction into medical practice as an alternative means of treating somatic pain and inflammatory processes.

**Key words:** herbal preparation, antinociceptive and antiexudative action, inflammation, somatic pain.

O.O. Нефьодов, Л.В. Еберле, А.О. Цісак, О.І. Гришук, О.І. Александрова, О.М. Гузенко,  
А.М. Шкодовська, І.Ю. Бурега

## ОЦІНКА АНТИНОЦИЦЕПТИВНОЇ ТА АНТИЕКСУДАТИВНОЇ ДІЇ КОМПЛЕКСНОГО ФІТОПРЕПАРАТУ В ТЕРАПІЇ СОМАТИЧНОГО БОЛЮ ТА ЗАПАЛЕННЯ РІЗНОГО ГЕНЕЗУ

Проведено експериментальні дослідження антиноцицептивної дії комплексного фітопрепарату на моделях соматичного болю індукованого термічним і хімічним подразниками та встановлення антиексудативної дії препарату на моделях запалення різного генезу. Дослідний зразок фітопрепарату представлений у вигляді мазі для трансдермального введення та містить комплекс рослинних екстрактів: *Juglans nigra L.*, *Acorus calamus L.*, *Styphnolobium japonicum L.* та *Zingiber officinale L.* Результати дослідження свідчать про ефективність засобу при терапії соматичного болю з пошкодженням шкірних покривів та при глибоких соматичних проявах больових реакцій. Активність фітозасобу не поступалась дії препарату порівняння. На трипсиновій та зимозановій моделях набряку комплексний фітопрепарат при трансдермальному введенні має виражену протизапальну активність, пригнічуючи активність циклооксигенази та ліпооксигенази, що робить його перспективним об'єктом для подальшого фармакологічного вивчення та впровадження в медичну практику як альтернативного засобу терапії соматичного болю та запальних процесів.

**Ключові слова:** фітопрепарат, антиноцицептивна та антиексудативна дія, запалення, соматичний біль.

*The study is a fragment of the research project "Pharmacological correction of simulated pathological conditions by using developed medicines" state registration No. 0122U200545.*

Pain and inflammation are one of the most common reactions of a living organism. They often lead to severe suffering and disability and, as a result, to decreased quality of life and sometimes to deaths among patients. Therefore, the problem of treating pain and inflammation is one of the most important tasks in medicine today.

Pharmacotherapy occupies one of the central places among modern methods of pain relief. A wide range of painkillers is used, among which narcotic and non-narcotic analgesics predominate. Narcotic pain relievers or opioid analgesics (morphine, fentanyl, buprenorphine, etc.), despite their effectiveness in severe acute and chronic pain, have regulated and limited use due to the possibility of causing severe side effects (physical and psychological dependence, respiratory depression, drug addiction, etc.). Non-narcotic analgesics (analgesics, antipyretics, nonsteroidal anti-inflammatory drugs (NSAIDs)), although not addictive, are characterized by moderate analgesic and anti-inflammatory effects, as well as a wide range of side effects (gastro-, hepato-, nephro-, hematotoxicity, etc.), which narrows the scope of their application. Recently, special attention has been paid to drugs of plant origin, which, compared to synthetic drugs, are safer under the conditions of long-term use for patients of different age categories and in the presence of concomitant chronic diseases [5, 6, 10, 11].

For the past ten years, the Department of Pharmacology and Drug Technology of the Odesa I.I. Mechnikov National University has been engaged in researching the pharmacognostic composition of medicinal plants of Ukraine, selecting optimal conditions for the extraction of plant raw materials with maximum preservation of biologically active substances, studying the pharmacological activity of plant extracts and creating herbal preparations based on them within the framework of the department's research project.

Our previous studies have shown that medicinal plants' phytochemical composition and ratio provide plant extracts with certain types of pharmacological activity. The study of the chemical composition and pharmacological activity of individual medicinal plants allows the subsequent creation of herbal preparations by combining different types of plants, which contributes to the expansion of the range of pharmacological action and effectiveness of the drug, both under conditions of oral administration and transdermal use [7–8].

**The purpose** of the study was to establish the antinociceptive and antiexudative effect of a complex herbal preparation for the treatment of somatic pain and inflammation of various genesis under the conditions of transdermal administration.

**Materials and methods.** Experimental studies were carried out on white non-linear rats and mice, which were kept on the standard diet of the Odessa I.I. Mechnikov National University vivarium with free access to food and water [1, 4]. Commission on Bioethics of the Odesa I.I. Mechnikov National University established that the performed scientific research on experimental animals meets the ethical requirements according to the order of the Ministry of Health of Ukraine No. 231 dated November 1, 2005. The study was carried out in accordance with the principles of the Declaration of Helsinki, adopted by the General Assembly of the World Medical Association (2000), the Convention of the Council of Europe on Human Rights and Biomedicine (1997), the relevant provisions of the WHO, the International Council of Medical Scientific Societies, the International Code of Medical Ethics (1983), General ethical principles of experiments on animals, approved by the First National Congress on Bioethics (Kyiv, 2001) in accordance with the provisions of the European Convention for the Protection of Vertebrate Animals Used in Experiments and Other Educational Purposes (Strasbourg, March 18, 1986) [4].

The object of research was a herbal preparation developed at the department, with the conventional name “Prodar”, which included plant extracts: *Juglans nigra* L. (black walnut), *Acorus calamus* L. (*Calamus vulgaris*), *Styphnolobium japonicum* L. (*Sophora japonica*) and *Zingiber officinale* L. (regular ginger) in a ratio of 7:3:4:1, respectively. The herbal preparation was made as an ointment for transdermal administration. The ointment base for the herbal preparation was made from polyethylene glycol-1500, polyethylene oxide-400 and 1,2-propylene glycol in a ratio of 3:4:2, respectively.

To study the antinociceptive effect of the herbal preparation, thermal (“Tail-immersion test in rats” and “Hot plate”) and chemical (formalin test) pain models were chosen, according to the methods of preclinical study of medicinal products [1]. Transdermal administration of the herbal preparation in all pain models was performed 15 minutes before the start of the experiment. Anesthetin ointment (produced by JSC “Lubnyfarm”) was used as a comparison drug.

Anti-exudative activity was studied on zymosan and trypsin models of inflammation. Dolgit cream (manufactured by Dolgort GmbH and Co. KG) was chosen as a comparison drug [1, 3, 7].

For each inflammation model, 4 groups of animals with 10 individuals each were created: Group 1 – control; Group 2 – received ointment base applications; Group 3 – received a complex herbal preparation; Group 4 – drug-comparison Dolgit cream.

The dynamics of changes in the inflammatory process were evaluated before administering the inflammatory inducer and after introducing the phlogogenic agent by measuring the volume and thickness

of the affected limb. The herbal preparation was applied after each measurement in a dose of 150 mg/cm<sup>2</sup> to the surface of the affected limbs. Volume increase (1) and anti-exudative activity were calculated for all groups of animals.

The volume increase (VI) of the limb was calculated according to the formula:

$$VI = ((O-I)/I) * 100$$

Where: V is the volume of the paw after the administration of the inflammatory inducer;

I – is the volume of the paw before administering the inducer.

Antiexudative activity (AA) was calculated according to the formula:

$$AA = 100 - (((V-I)/I_s) / ((V-I)/I_c)) * 100$$

where: AA – antiexudative activity;

s – study group;

c – control group.

Methods of statistical analysis processed all the obtained data generally accepted in medical and biological research using standard computer program packages. Mathematical processing included calculations of arithmetic mean values (M) and their errors ( $\pm m$ ). Reliability between-group differences in the pain response threshold indicator's values were established using the Student's parametric t-test, the Wilcoxon rank-sum test, the Mann-Whitney criterion, and the one-factor analysis of variance (ANOVA) method. Differences were considered statistically significant at the level of  $p \leq 0.05$ . Before applying parametric criteria, the hypothesis of the normal distribution law of random variables was tested [2].

**Results of the study and their discussion.** According to the study results, the latent period in animals of the control group in the “Hot plate” test was 7.3 s on average, while in the “Tail-immersion test in rats”, – it was 9.9 s. Similar parameters were observed in the animals that received applications of the ointment base.

Transdermal administration of a test sample of a complex herbal preparation effectively reduced the threshold of nociceptive response to thermal irritation in animals, both in the “Tail-immersion test in rats” test (15.4 $\pm$ 0.9 s) and in the “Hot plate” test (17.7 $\pm$ 1.2 s.), which exceeded the indicators of the control group by 110.9 % and 78.8 %, respectively. It should be noted that the effectiveness of the herbal preparation did not significantly differ from the comparison drug.

The next stage of our study was to establish the analgesic activity of a complex herbal preparation in a formalin-induced test, which is the registration of the nociceptive response of rodents to the induction of pain caused by formalin tissue damage (somatic deep pain).

According to our studies, it was shown that in the formalin test, the prototype of the herbal preparation significantly ( $p \leq 0.05$ ) reduced the manifestations of pain response compared to the control by 45.2 % in the first phase and 68.6 % in the second phase. It should be noted that in the second phase of the experiment, the nociceptive activity of the drug significantly ( $p \leq 0.05$ ) exceeded even the indicators of the comparison drug – Anesthesin (58.9 $\pm$ 3.5) and amounted to 31.4 % in relation to the control (Table 1).

Table 1

**Analgesic activity of the experimental sample of the herbal preparation on thermal and chemical models of pain**

Pain models	Studied parameters	Animal groups				
		1	2	3	4	
Tail-immersion test in rats	Latent period, seconds	7.3 $\pm$ 0.6	7.5 $\pm$ 0.4	15.4 $\pm$ 0.9*	16.1 $\pm$ 1.2*	
	in % to control	100	102.7	210.9*	220.5*	
Hot plate test	Latent period, seconds	9.9 $\pm$ 0.8	9.5 $\pm$ 0.6	17.7 $\pm$ 1.2*	17.3 $\pm$ 1.5*	
	in % to control	100	95.9	178.8*	174.7*	
Formalin-induced pain test	Phase I	Reaction time, s	65.3 $\pm$ 4.1	67.5 $\pm$ 5.6	35.8 $\pm$ 2.5*	29.5 $\pm$ 2.2*
		in % to control	100	103.4	54.8*	43.7*
	Phase II	Reaction time, s	177.3 $\pm$ 8.1	176.0 $\pm$ 9.6	55.7 $\pm$ 4.4*	58.9 $\pm$ 3.5*
		in % to control	100	99.2	31.4*	33.2*

Note: \* – statistically significant difference compared to the control group ( $p \leq 0.05$ ).

The next stage was studying the antiexudative activity of the herbal preparation on zymosan and trypsin models of inflammation.

On the model of trypsin inflammation, in all groups of animals, during the first three hours after the phlogogen administration, the development of a local inflammatory reaction was noted, where the

increase in the volume and thickness of the affected limbs were, on average 42 % in relation to the initial indicators (Table 2, Fig. 1).

In the groups of animals that received transdermal applications of the complex herbal preparation and the comparison drug, an accelerated reduction of the inflammation centre was recorded from the 6th hour of the experiment with an approximation of morphological parameters of the affected limbs to the initial values at 24 hours, in contrast to the first and second groups of animals. The antiexudative activity of the herbal preparation at the 24th hour of the experiment was 67 % ( $p \leq 0.05$ ), and that of the comparison drug was 78.5 % ( $p \leq 0.05$ ) in relation to the control (Table 2).

Table 2

**Antiexudative activity of a complex herbal preparation on the model of trypsin and zymosan inflammation**

No.	Group	Trypsin inflammation			Zymosan inflammation		
		Observation time (hours)					
		1	3	24	1	3	24
Increase in volume, in % to the initial values							
1	Control	38.4 ±3.3	41.5 ±3.9	29.6 ±2.1	75.7 ±6.7	72.4 ±6.9	42.3±3.9
2	Ointment base	39.2 ±3.8	43.4 ±4.3	28.9 ±2.7	75.2±5.5	70.6±6.8	41.8±4.3
3	“Prodar” herbal preparation	38.8 ±3.8	42.7 ±4.3	11.4 ±0.8*	75.9±6.1	66.4±5.9	8.2±0.5*
4	Dolgit cream	38.6±2.9	40.4±3.6	6.3±0.5*	76.3±6.9	52.3±4.2*	14.5±1.1*
Antiexudative activity in % relative to the control							
3	“Prodar” herbal preparation	-	-	67±4.7*	-	4.3±0.2	65.2±6.1*
4	Dolgit cream	-	-	78.5±5.6*	-	12.2±1.1	58.3±4.9*

Note: \* – statistically significant difference compared to the control group ( $p \leq 0.05$ ).

The registration of the thickness of the affected limbs of rats, similar to the volume results, indicated a pronounced anti-inflammatory activity of the herbal preparation already after the first application, with a further effect after each repeated application to the focus of inflammation (Fig. 1).

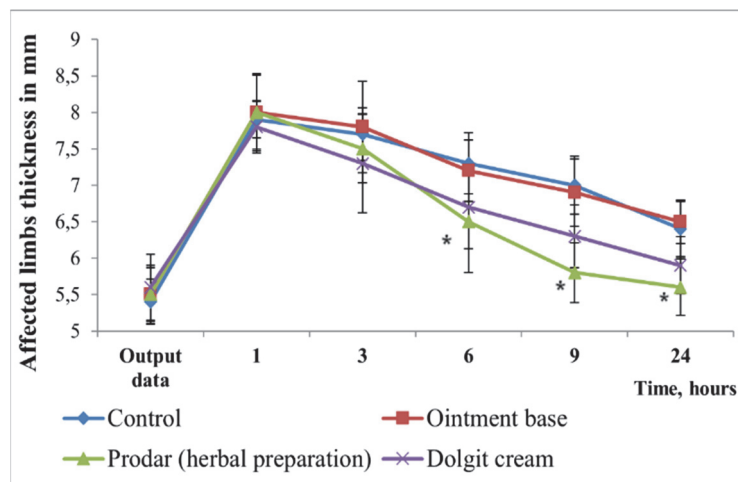


Fig. 1. Thickness of the affected limbs of rats (mm) after trypsin injection ( $M \pm m$ ,  $n=10$ ). Note: \* – statistically significant difference compared to the control group ( $p \leq 0.05$ ).

drug – Dolgit cream. The best anti-exudative activity of the complex herbal preparation was noted on the model of zymosan inflammation. Starting from the third hour of the experiment, the volume and thickness of the affected limbs of the animals decreased with a subsequent tendency to return to the initial results (Table 2, Fig. 2).

At 24 hours, the volume increase in the third group was 8.2 % relative to baseline values, and the anti-exudative activity was 65 % ( $p \leq 0.05$ ) relative to the control, while in the comparison group, it was 14.5 % and 58.3 %, respectively.

The inflammatory process was observed throughout the experiment in the control animals that did not receive basic treatment and in the group that received an ointment base. The animals of these groups

The most pronounced effect of the herbal preparation was noted, according to the thickness of the limbs of the animals, from the sixth hour of the experiment, when it was possible to visually note the reduction of redness and swelling of the limbs. During the 9th and 24th hours of the experiment, the animals moved freely in the cage and calmly responded without twitching to repeated applications of the ointment.

Against the background of trypsin inflammation, the indicators of the thickness of the affected limbs of animals that received the experimental sample of the herbal preparation were somewhat inferior to the action of the comparison

could not step on the affected limbs, where the induced swelling had a high temperature and a distinct red color for two days after the end of the experiment.

Registration of the thickness of the affected limbs of the animals showed that the herbal preparation after the first application contributed to the reduction of edema and the restoration of indicators, and starting from the sixth hour and during the following measurements, the effectiveness of the product, even exceeded the effect of the comparison drug. At 9 and 24 hours, the thickness of the affected limbs of the animals decreased by 12 % and 8 %, respectively, compared to Dolgit cream and by 22 % and 18 % compared to the control group (Fig. 2).

It should be noted that, according to the morphological parameters (thickness and volume) of the animal limbs, the studied sample of the herbal preparation exceeded the anti-inflammatory activity of the comparison drug, which positions the drug as a lipoxygenase inhibitor.

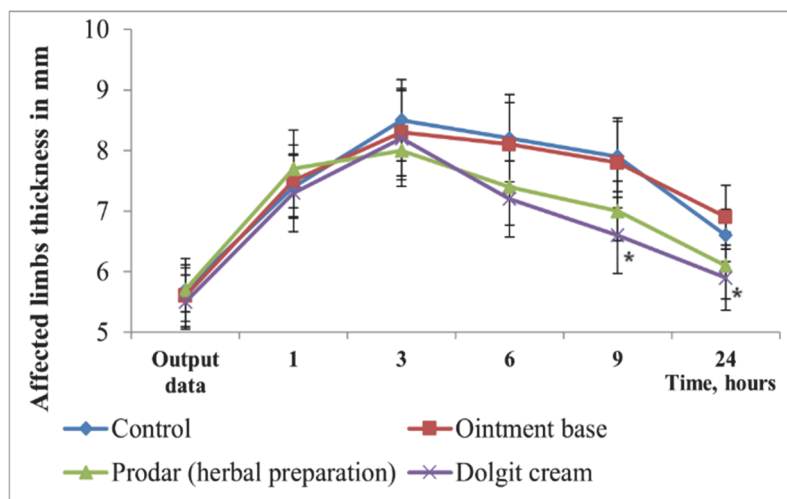


Fig. 2. Thickness of affected limbs of rats (mm) after zymosan injection ( $M \pm m$ ,  $n=10$ ). Note: \* – statistically significant difference compared to the control group ( $p \leq 0.05$ ).

herbal preparation was higher in the study's second phase than in the first. This indicates a moderate effect of the agent on nociceptors, which are activated in the first phase, and a pronounced effect on the inflammatory process in the second phase of the test. Transdermal administration of the herbal preparation in the second phase of the formalin test affects the functions of the neurons of the posterior horns of the gray matter of the spinal cord, where the neurons of the pain ascending pathways lie. Therefore, the presence of anti-inflammatory and pain-relieving effects of the herbal preparation was noted in the animals of this group.

To establish in more detail the antiexudative effect of the complex herbal preparation and the mechanism of action, a study was conducted on trypsin and zymosan models of inflammation. It is known that the trypsin inflammation model belongs to the group of short-acting inflammatory processes. Trypsin as a phlogogen leads to the activation of protein-activating 2-receptors, which leads to the synthesis of cyclooxygenase-2. Zymosan can disorient and translocalize phospholipid membranes, which provokes calcium flow into the cell and hydrolysis of membrane phospholipids, resulting in the release of arachidonic acid along the lipoxygenase pathway of metabolism with the formation of leukotrienes and other products of the inflammatory process [1, 3, 7].

As a result of the study, it can be concluded that the herbal preparation is an effective means of correcting nociceptive somatic pain and exhibits quite pronounced anti-inflammatory activity on the model of zymosan and trypsin edema, affecting the leukotriene and prostaglandin phases of inflammation due to the presence of a complex of biologically active compounds in the composition of medicinal plants. The trypsin model of inflammation shows that the herbal preparation not only inhibits the cyclooxygenase pathway of arachidonic acid metabolism, which leads to a decrease in the synthesis of prostacyclin prostaglandins and inhibits the release of inflammatory mediators by leukocytes but is also capable of influencing the activation of protein-activating 2-receptors.

Thus, a pilot sample of a complex herbal preparation for transdermal use is a promising tool for further study and introduction into therapy as an adjuvant for nociception of somatic and inflammatory origin.

Thermal and chemical models of pain are the basis for studying antinociceptive activity in drugs that suppress somatic superficial pain (in case of damage to the skin on thermal tests) and deep acute pain caused by a chemical stimulus – formalin. According to our study, it has been proven that the complex herbal preparation can effectively lower the pain threshold on thermal models of pain, which indicates the activity of the remedy in superficial somatic types of pain and does not significantly differ from the action of the comparison drug. In the formalin test, the activity of the

### Conclusions

1. The complex herbal preparation demonstrates a pronounced antinociceptive effect in the therapy of somatic pain, both in case of damage to the skin by thermal irritants (by 110.9 % and 78.8 % ( $p \leq 0.05$ )) and in conditions of deep acute pain induced by a chemical phlogogen (by 45.2 % in phase I and by 68.6 % in phase II ( $p \leq 0.05$ )).

2. The experimental sample of the herbal preparation shows a pronounced reliable ( $p \leq 0.05$ ) anti-exudative effect on the models of trypsin (67 % compared to the control) and zymosan (65.2 % compared to the control) models of inflammation, which indicates the ability of the complex of biologically active substances included in the product to inhibit inflammation on the cyclooxygenase and lipoxygenase pathways of metabolism.

3. The established antinociceptive and antiexudative activity of the complex phytopreparation justifies conducting further pre-clinical and clinical studies to expand the indications for using the investigated drug.

*Prospects for further research consist in the continuation of scientific work to establish all possible pharmacokinetic and pharmacodynamic interactions between the components of the herbal preparation and the features of its use in complex pharmacotherapy of pain of somatic and inflammatory origin.*

### References

1. Doklinichni doslidzhennya likarskykh zasobiv; za red. A. V. Stefanova. Kyiv: Avitsenna, 2001. 528 s. [in Ukrainian]
2. Lutsenko RV, Sydorenko AH, Koyro OO. Doslidzhennya orhanoprotektoynykh vlastyvostey 2-hidroksy-naftalen-1-il-2-(2-okso-1,2-dyhydro-indol-3-iliden)-atsetamidu. Svit medytsyny ta biolohiyi. 2021; 2 (76). 223–226. [in Ukrainian]
3. Nefodov OO, Myasoyed YuP, Solomenko MV, Velykorodna-Tanasychuk OV, Baklunov VV, Adehova LYa. ta in. Vyvchennya korektsiyi somatychnoho bolyu za umov eksperimentalnoyi patolohiyi rozsiyanoho sklerozy. Ukrayinskyy zhurnal medytsyny, biolohiyi ta sportu. 2021; 6(6): 66–73. [in Ukrainian]
4. Tverdokhlib IV, Marchenko DH. Ultrastrukturni zminy skorotlyvoho aparatu miokarda shlunochkiv shehuriv na etapakh prenatalnoho ontogenezu v normi ta pislya diyi alkoholyu. Svit medytsyny ta biolohiyi. 2019. 3 (69); 225–230. [in Ukrainian]
5. Bernard A, Barreneche T, Lheureux F. Analysis of genetic diversity and structure in a worldwide walnut (*Juglans regia* L.) germplasm using SSR markers. PLoS One. 2018; 13(11): 67–76. doi.org/10.1371/journal.pone.0208021
6. Duyun IF, Mazulin OV, Mazulin GV. Chemical composition of polyphenolic compounds in the grass yarrow (*Achillea micranthoides* klok.). Pharmaceutical journal. 2020; 75(1): 80–87. doi.org/10.2298/10.32352/0367-3057.1.20.09
7. Kravchenko IA, Eberle LV, Kobernik AO, Nesterkina MV. Anti-inflammatory and analgesic activity of ointment based on dense ginger extract (*Zingibe officinale*). Journal of Herbmed Pharmacology. 2019; 8(2); 126–132. doi:10.15171/jhp.2019.20
8. Kravchenko IA, Kobernik AA, Eberle LV. Optimization of extraction methods for total polyphenolic compounds obtained from rhizomes of *Zingiber officinale*. Trends in Phytochemical Research. 2018; 2(1): 37–42. doi.org/10.1001.1.25883623.2018.2.1.5.3
9. Krvavych AS, Petrina RO, Suberlyak SA. Preparation and research of *Salendula officinalis* callus biomass extracts. Chemistry, technology of substances and their application. 2018; 1(2): 63–68. doi.org/10.23939/ctas2018.02.063
10. Trandafir I, Cosmulescu S, Botu M. Antioxidant activity, and phenolic and mineral contents of the walnut kernel (*Juglans nigra* L.) as a function of the pellicle color. Fruits. Food Chem. 2016; 71: 177–184. doi.org/10.1051/fruits/2016006.
11. Vieira V, Prieto MA, Barros L. Optimization and comparison of maceration and microwave extraction systems for the production of phenolic compounds from *Juglans regia* L. for the valorization of walnut leaves. Ind. Crops Prod. 2017; 107: 341–352. doi.org/10.1016/j.indcrop.2017.06.012

Стаття надійшла 30.08.2022 р.