

Study of specific pharmacological activity of standardized composition of bee product substances for treatment of urogenital system

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Introduction. The work presents review of the data literature, which indicate the prospects of creation new highly efficient drugs for the treatment of chronic prostatitis and prostate gland adenoma based bioactive standardized substances of bee products, including powdered honey (PH), propolis phenolic hydrophobic drug (PPHD) and bee pollen (BP).

Materials and methods. Results of discussion of preclinical pharmacological studies of standardized substances of bee products composition – PH, PPHD and BP for the treatment of specified pathology is given in the experimental part.

Results. It was found that the most pronounced anti-inflammatory effect on the level 40 % the mixture of APIs (PH, PPHD and BP) detects at a dose of 100 mg/kg in relation to the reference drug – trianom capsules in doses of 100 and 130 mg/kg.

Conclusions. Usage of bee products is grounded in creation of the new drug on their basis in the form of standardized substances of bee products composition –PH, PPHD and BP for chronic prostatitis and prostate gland adenoma. It was found that the most pronounced anti-inflammatory effect on 40 % the mixture of APIs (PH, PPHD and BP) detects at a dose of 100 mg/kg. It was established that the composition of standard substances of bee products – PH, PPHD and BP at a dose of 100 mg/kg shows a more pronounced specific pharmacological effect in comparison to the reference product – trianom capsules at doses of 100 and 130 mg/kg, which positively affect the course of the pilot prostatitis in male rats caused by dichloroethyl.

Ключові слова:

захворювання органів сечостатевої системи, мед, прополіс, обніжжя бджолине, апітерапія.

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Дослідження специфічної фармакологічної дії композицій стандартизованих субстанцій продуктів бджільництва для лікування захворювань органів сечостатевої системи

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У роботі наведені дані огляду фахових літературних джерел, що свідчать про перспективність створення нових високо-ефективних лікарських засобів для лікування хронічних простатитів та аденоми передміхурової залози на основі біологічно активних стандартизованих субстанцій продуктів бджільництва, зокрема меду порошокоподібного (МП), фенольного гідрофобного препарату прополісу (ФГПП) та обніжжя бджолиного (ОБ).

Матеріали та методи. В експериментальній частині представлені результати обговорення доклінічних фармакологічних досліджень композиції стандартизованих субстанцій продуктів бджільництва – МП, ФГПП та ОБ для лікування вказаної патології.

Результати. Згідно з результатами досліджень, встановлено, що найвираженішу протизапальну дію на рівні 40 % суміш АФІ (МП, ФГПП та ОБ) виявляє у дозі 100 мг/кг щодо референс-препарату – капсул трианом у дозах 100 та 130 мг/кг.

Висновки. Обґрунтовано використання продуктів бджільництва для створення на їх основі нового лікарського препарату у формі композиції стандартизованих субстанцій продуктів бджільництва – МП, ФГПП та ОБ для лікування хронічних простатитів та аденоми сечостатевої залози. Встановлено, що найбільш виражену протизапальну дію на рівні 40 % суміш АФІ (МП, ФГПП та ОБ) виявляє у дозі 100 мг/кг. Встановлено, що композиція стандартизованих субстанцій продуктів бджільництва – МП, ФГПП та ОБ у дозі 100 мг/кг проявляє набагато вираженішу специфічну фармакологічну дію щодо референс-препарату – капсул трианом у дозах 100 та 130 мг/кг, що позитивно впливає на перебіг експериментального простатиту в щурів-самців, котрий викликаний дихлоретиллом.

Ключевые слова:

заболевания органов мочеполовой системы, мёд, прополис, обножки пчелиные, апитерапия.

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Исследование специфического фармакологического действия композиции стандартизованных субстанций продуктов пчеловодства для лечения заболеваний органов мочеполовой системы

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В работе приведены данные обзора научных литературных источников, которые свидетельствуют о перспективности создания новых высокоэффективных лекарственных средств для лечения хронических простатитов и аденомы предстательной железы на основе биологически активных стандартизованных субстанций продуктов пчеловодства, в частности мёда порошокобразного (МП), фенольного гидрофобного препарата прополиса (ФГПП) и пчелиной обножки (ОБ).

Материалы и методы. В экспериментальной части представлены результаты обсуждения проведённых доклинических фармакологических исследований композиции стандартизованных субстанций продуктов пчеловодства – МП, ФГПП и ОБ для лечения данной патологии.

Результаты. По результатам исследований установлено, что наиболее выраженный противовоспалительный эффект на уровне 40 % смесь АФИ (МП, ФГПП и ОБ) обнаруживает в дозе 100 мг/кг по отношению к референт-препарату – капсулам трианом в дозе 100 и 130 мг/кг.

Выводы. Обосновано использование продуктов пчеловодства для создания на их основе нового лекарственного препарата в форме композиции стандартизированных субстанций продуктов пчеловодства – МП, ФГПП и ОБ для лечения хронических простатитов и аденомы половой железы. Установлено, что наиболее выраженное противовоспалительное действие на уровне 40 % смесь АФИ (МП, ФГПП и ОБ) обнаруживает в дозе 100 мг/кг. Установлено, что композиция стандартизированных субстанций продуктов пчеловодства – МП, ФГПП и ОБ в дозе 100 мг/кг проявляет более выраженное специфическое фармакологическое действие по отношению к референт-препарату – капсулам трианом в дозе 100 и 130 мг/кг, что положительно влияет на течение экспериментального простатита у крыс-самцов, вызванного дихлорэтилом.

Introduction

In the current conditions in the treatment of the genitourinary system diseases prostatitis is one of the most common diseases in men of reproductive age [1]. For example, according to the urology service of Ukraine chronic prostatitis now affects about 30–45 % of men, of which almost 80 % are patients aged 21 to 56 years, and 60–75 % are of age 31 to 50 years [2]. Wide distribution of the disease indicates insufficient study of its etiology and pathogenesis, steady progress, and the lack of effective schemes and methods of diagnosis and treatment [3].

Usually, prostatitis, which is an inflammation (swelling) of the prostate gland tissue is characterized by a steady progress, with exacerbation of which patients complain of constant pain in the abdomen, urinary disorders, sexual function (sexual dysfunction), ejaculation and changes in the quantity and quality of the last [4]. The appearance of these symptoms is usually associated with infection, sexually transmitted diseases, immunity disorders, frequent hypothermia, stress, allergic violation status, hormonal imbalance et al., the further development of which in some cases leads to the formation of chronic forms, accompanied by corresponding consequences and prolonged treatment [1,3,4].

Pharmacotherapy of prostatitis depends largely on the severity of the disease, its duration and disturbances of sexual function. Etiological factors (infection, hormonal disorders) are critical in choosing specific ways of treatment. In this regard, at this pathology nitrofurans derivatives, nevyhramon, antibiotics are usually prescribed from the number of drugs, taking into consideration the sensitivity of microflora, sown from prostate secretions. In addition, one of the basic drugs of natural origin – prostatilen is also successfully used the treatment of patients with prostatitis [5], the active ingredient of which is selected from of the prostate gland of bulls, which is a combination of proteins that, like other citomedines, are able to influence the state of the main homeostasis systems.

Recently, considerable attention is given to wide application of bee products in the treatment of prostatitis and prostate gland adenoma [6–8], in particular, natural honey, propolis and bee pollen (flower pollen) (BP), and their standardized substances and officinal drugs in combination with chemo- and phytodrugs. It is considered that the use apiproducs and their agents in the diseases of the genitourinary system is a very important component of drug therapy as biologically active compounds have several advantages over synthetic drugs and due to their complex structure contribute versatile effects on macro organism.

Honey is a natural complex of biologically active substances, similar in composition to blood plasma, and, therefore, it shows high healing properties. First of all, valuable medicinal and nutritional properties of honey are caused by its composition containing 200 important for the body substances: carbohydrates, proteins, enzymes, amino acids, vitamins, minerals and others. However, the content of biologically active compounds in different types of honey can vary depending

on several factors, therefore, natural honey requires standardization for its introduction into medical practice.

Another value is a propolis and its compounds. Propolis is a glue collected by bees from buds of trees and grass that bees use to strengthen and disinfection of their hundreds. Propolis is a complex multicomponent system of biologically active substances, which includes more than 50 different in nature substances. The main groups of propolis is resin, balms, essential oils and waxes, as well as minerals, vitamins, amino acids (8 to 17) and others. It was found that flavonoids takes more than 25 % among all components of propolis [7].

Preparations of propolis exhibit a wide range of biological activities: antimicrobial, regenerating, immune-stimulating, anti-inflammatory, reparative, wound healing, hepatoprotective, membrane stabilizing [9–11]. Due to its multidirectional pharmacological action, its usage is possible in urology, especially for the treatment of prostatitis and prostate gland adenoma [7]. In this regard, among the number of standardized propolis substances, special attention deserve propolis phenolic hydrophobic drug (PPHD) and bee pollen (BP), for which the relevant methods of quality control (MQC) were developed.

Substance BP is a finely dispersed powder from white to brown colour, depending on the plants from which bees collect nectar, which includes a large number of proteins, carbohydrates, lipids, nucleic acids, mineral elements and other biologically important substances [8]. In addition, BP composition includes essential amino acids and essential unsaturated fatty acids – linoleic and linolenic, which quantities is more than half of the total amount of these compounds.

Phospholipids of bee pollen are represented with choline-phosphoglycerides (lecithins) inositolphosphoglycerides, etanolaminophosphoglycerides (cephalins), phosphatidylserines and other compounds that make up the semi dense cell membranes of animal and humans organisms that selectively regulate flow of ions to the cells and are actively involved in metabolism. Showing the properties of substances with lipotropic action phospholipids promote the emergence slowdown and excessive accumulation of fat and its deposition in the cells, especially liver tissue, which prevents fatty liver and atherosclerosis [8].

The presence of a significant amount of phytosterols, carbohydrates, enzymes, nucleic and triterpene acids, vitamins and other biologically active substances in BP provides anti-inflammatory, wound healing, cardiotoxic, antiatherosclerotic and other pharmacological actions.

Thus, the data above indicate the prospects of new highly efficient drugs for the treatment of chronic prostatitis and prostate gland adenoma based on biologically active standardized substances of bee products, including powdered honey (PH) PPHD and BP in order to replenish the pharmaceutical market of Ukraine with new national drugs.

The aim of this work was the discussion of the obtained results of conducted preclinical pharmacological studies of the new national drug of natural origin for the treatment

of diseases of the genitourinary system, including prostatitis and prostate gland adenoma.

Materials and methods

The objects of research were standardized substances of bee products – PH, PPHD and BP and their mixture as the API composition that are the part of the developed drug.

Powdered honey (PH) (TC U 10.8-39834691-001:2015 «Honey powdered») [12,13]. The dry, fine powder without impurities, dry, smooth consistency and pleasant taste without other flavours and smells, homogeneous throughout the mass with different shades of colour depending on the raw material.

Mass fraction of moisture and volatile substances is less than 8.0 %. Mass share of renewable carbohydrates (to anhydrous substance) is not less than 70.0 %. Mass fraction of sucrose (to anhydrous substance) is less than 6.0 %. Diastase number Goethe units (calculated on the anhydrous substance) is at least 15.0. 5-hydroxymethylfurfural content (calculated on dry residue) is less than 0.008 % (80 ppm). Acidity (milliequivalents of sodium hydroxide 0.1 mol/dm³) is less than 50.0 per 1 kg. The content of proline (calculated on the anhydrous substance) is not less than 0.03 %. Mass fraction of ash is not more than 7.0 %. Size of grinding: sieve residue on the number of wire mesh N. 067 is less than 1.0 %. Mass fraction of impurities: metallomagnetic (the size of the largest linear dimension of less than 0.3 mm) is less than 3·10⁻⁴; mineral, not soluble in hydrochloric acid, is less than 1.0 %; vegetable – is not allowed.

MP is obtained from natural honey by the method of activation drying by YUVET technologies [14] or by the method of freeze-drying (moisture release from the frozen solution) using authorized for the use excipients [13].

The substance comes in powder form designed for usage in pharmaceutical, perfumery and cosmetic, and food industries and must meet the developed and approved by the relevant authorities requirements TC U 10.8–39834691–001:2015 «Powdered honey» [13].

Propolis phenolic hydrophobic drug (PPHD) (Praeparatum Propolis phenohydrophobum) – (RC № UA/4505/01/01, Order MH Ukraine № 337 from 07.06.2011, PhA 42Y-34-20-95, AND-DV-GF-090, Specification SPC-PP-77. Producer: «Zdorovya» Pharmaceutical company, Ltd. (Kharkiv, Ukraine) [2].

PPHD is hydrophobic powder of reddish-brown colour, specific odour, soluble in 96 % alcohol P, practically insoluble in water P, petroleum ether P, chloroform P. Content of phenolic compounds calculated on the dry matter should be at least 50.0 %. The loss in weight on drying is not more than 3.0 %, heavy metals are less than 0.001 %.

The main BAS of PPHD that cause its pharmacological effects are phenolic compounds, including apigenin, luteolin, kaempferol, quercetin, robidanol and others [7].

Bee pollen (flower pollen) – (DSTU 3127-95) (AND-DR-ZT-DF-029) (for the incoming control). Producer: «Zdorovya» Pharmaceutical company, Ltd. (Kharkiv, Ukraine) (Order MH Ukraine from 23.05.2008 № 273. RC № UA/8194/01/01) [2].

The collected by bees pollen has a dense texture in the form of lumps. They are solid in consistency, with irregular shape, weight from 5 to 20 mg, colour from light yellow to brown, a specific characteristic smell, sweet taste, the concentration of hydrogen ions (pH) of 2 % aqueous solution product is (4.3–5.3) – 4.7. The chemical composition of the collected

pollen differs significantly from collecting pollen and is characterized by a high content of various groups of biologically active compounds [8].

Study of preclinical pharmacological research of the developed drug was conducted at the Central Research Laboratory of the National University of Pharmacy.

Considering that chronic prostatitis and prostate gland are often accompanied by inflammation and pain during studying of specific pharmacological activity of standardized substances mixture of bee products (PH, PPHD and BP) to establish the effective dose of the composition there was selected the model of acute inflammation exudative carrageenin foot inflammation in rats [15]. Various mediators of inflammation are involved in the mechanism carrageenin edema, according to Di Rosa et al. [16] in the first 30–90 minutes in the pathogenesis of edema is caused by histamine and serotonin, in the range between 1.5–2.5 h – by kinines, and between 2.5–5.5 h – by prostaglandins. The range of mediators involved in the development of the process of exudation in this model allows to assume the mechanism of action of the studied substances.

Experiments were carried out on rats weighing 150–170 g. Edema of the foot was caused with subplantare introduction into the right hind paw 0.1 ml 1 % solution of carrageenin manufactured by Serva. The composition of standardized substances of PH, PPHD and BP was administered in doses 5, 30, 60 i 100 mg/kg. Voltaren gel was used as the reference drug with anti-inflammatory action at a dose of 8 mg/kg (LD₅₀ by antiexudative effect in this model) [17]. Diclofenac sodium is widely used in the clinic of internal diseases accompanied by inflammation [18]. The studied drug and the reference drug were administered intragastrically one hour before the injection of flohogenic agent. Animals of the control pathology group received adequate to their mass quantity of water. The development of edema was registered by the increase of paws volume, which was measured in the dynamics through 1, 2, 3, 5, 24 hour with onkometre by Zaharevskyy A. S. [19,20]. Anti-inflammatory activity was determined by the degree of reduction of edema in animals treated with drugs compared with animals of control pathology group and expressed as a percentage. The results of the experiment were calculated according to the formula presented in Fig. 1:

$$A (\% \text{ oppression}) = \frac{V_k - V_0}{V_k} \times 100 \%,$$

where V_k – the average value of paw volume in the group of control pathology;

V_0 – the average value of paw volume in the groups treated with the composition of standardized substances.

In view of the established dynamic antiexudative action of standardized substances of bee products composition it can be assumed that their BAS are relatively quickly absorbed into the bloodstream and eliminated relatively slowly, which may contribute to the treatment of acute and chronic inflammation typical for prostatitis.

In this regard, it became feasible to conduct a study of anti-prostatic activity to study the effect of the composition of API (PH, PPHD and BP) mixture on the course of experimental prostatitis, which was were carried out on a model of acute prostatitis in rats caused by dichloroethyl [21].

For screening there were chosen the following doses – 50, 100, 130 and 170 mg/kg. As a reference drug the medical analogue – trianom capsules – were used at a dose of 6 mg/kg,

Table 1. The results of screening studies of antiprostatic activity of standardized substances of bee products composition – PH, PPHD and BP (n = 6)

Indicator	Groups of animals					
	Intact control	Control pathology	Triamol 6 mg/kg	The mixture API 50 mg/kg	The mixture API 100 mg/kg	The mixture API 130 mg/kg
	x ± Sx					
Leucocytes, 109/l	14.55 ± 1.81	22.30 ± 1.40*	12.56 ± 1.31**	17.60 ± 1.67	12.85 ± 1.64**	14.05 ± 1.75**
MDA in serum, mmol/l	0.29 ± 0.03	0.72 ± 0.11*	0.44 ± 0.04**	0.59 ± 0.19	0.4 ± 0.03**	0.61 ± 0.09
MDA in prostate homogenate, mmol/g	25.64 ± 2.69	46.66 ± 3.59*	24.61 ± 3.02**	44.36 ± 6.02	27.43 ± 3.52**	25.32 ± 3.12**
Weight coefficient of vesicles gland	1.14 ± 0.10	0.42 ± 0.04*	0.80 ± 0.04*/**	0.53 ± 0.07*/***	0.54 ± 0.03*/**/****	0.60 ± 0.04*/**/****

*: probable deviations in relation to the intact control group, p < 0.05; **: probable deviations relative to the control pathology group, p < 0.05;

***: probable deviations in relation to the reference drug group (trianom), p < 0.05.

which was calculated using the coefficient of species stability by Rybolovlev [16]. Active substance of trianom capsules is an active lipid-sterol complex of herbal origin.

Outbred white male rats weighing 250–290 g were used in experiment. On day 10 of the experiment blood was taken in rats from the tail vein for clinical analysis. After the procedure the rats were decapitated under ether anesthesia. Vesicles glands were weighed, and their weight coefficient was calculated. In serum and prostate homogenate malondialdehyde content was determined because it is known that the system is activated lipid peroxidation when prostatitis [22]. Results obtained are presented in Table 1.

Results and their discussion

Analysis of the obtained results, presented in Fig. 1, shows that the most effective anti-inflammatory composition of API mixture reveals at a dose of 100 mg/kg. The average anti-inflammatory activity of the mixture of PH, PPHD and BP at the dose 100 mg/kg was 40 % during the experiment. In the given dose the drug significantly reduced the development of edema during the experiment compared to the control pathology group, but its activity did not exceed the anti-inflammatory effects of diclofenac sodium, which also significantly reduced edema during the experiment.

Considering the data set by Di Rosa [16], about the established sequence of inflammatory mediators changes in this pathology model it can be assumed that the mechanism of anti-inflammatory action of standardized substances of bee products is based on their ability to inhibit the synthesis of prostaglandins, which are important in the treatment of prostate diseases, which are often accompanied by pain syndrome [23]. It is also possible to suggest that effect is the result of complex action of flavonoids, which are present in the API mixture composition, on cells and enzymes responsible for the development of inflammation. It is known that phenolic compounds exhibit antioxidant properties [24], in connection with what ability of mixture PH, PPHD and BP to block induction of lipid peroxidation, which occurs during inflammation, is related [25].

The results presented in Table 1 show that under experimental pathology in rats following signs of inflammation were observed. On the 10th day after the alteration in the prostate gland areas of necrosis, purulent discharge, reduction of weight of vesicles glands were observed.

In conditions of treatment with the composition of standardized substances of bee products in doses of 100 and 130 mg/kg, trianom capsules, likely reduction in leucocytes level in the blood and the likely increase of weight coefficient of vesicle glands were observed, prostate gland was of normal type form without cell necrosis in the most animals. Local activation of lipid peroxidation and reduced antioxidant capacity

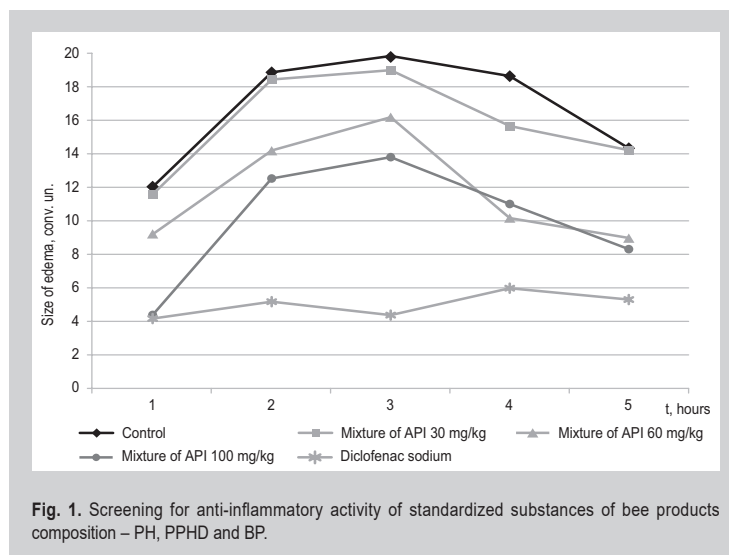


Fig. 1. Screening for anti-inflammatory activity of standardized substances of bee products composition – PH, PPHD and BP.

in prostate gland tissue play an important pathogenic role in the development of chronic prostatitis.

The pathology was characterized by the increased levels of MDA in blood serum and prostate homogenate, indicating the activation of lipid peroxidation and the development of inflammation. Analysis of the results obtained in groups of animals treated with standardized substances of PH, PPHD and BP composition in doses of 100 and 130 mg/kg showed probable reduction of malondialdehyde in prostate homogenate compared to the control pathology group. In the group of animals treated standardized substances of PH, PPHD and BP composition in doses of 100 and 130 mg/kg MDA levels in serum compared with the control pathology group significantly reduced. Group of animals treated with trianom in the dose of 6 mg/kg, also showed a likely reduction in leucocytes in the blood, malondialdehyde in serum and prostate homogenate, the likely increase of weight coefficient of vesicles gland compared with the control pathology group.

Thus, in condition experimental prostatitis composition of standardized substances of bee products – PH, PPHD and BP, in the dose of 100 mg/kg, it was revealed a pronounced therapeutic effect at the level of the reference drug – trianom capsules.

Conclusions

1. The application of bee products to create a new drug on their basis in the form of standardized substances of bee products composition – PH, PPHD and BP for chronic prostatitis and prostate gland adenoma was grounded.

2. It was found that the most pronounced anti-inflammatory effect on 40 % level detects the mix-ture of API (PH, PPHD and BP) at the dose of 100 mg/kg.

3. It was established that the composition of standardized substances of bee products –PH, PPHD and BP, ta the dose of 100 mg/kg shows maximally pronounced specific pharmacological effect related to the reference drug – trianol capsules at the doses of 100 and 130 mg/kg, which posi-tively affects the course of experimental prostatitis in male rats caused by dichlorethyle.

Perspectives of further scientific research. Composition of standardized substances of bee products – PH, PPHD and BP, are a promising source for development of new domestic drugs for use in urological practice. The presented results of the studies confirm the necessity of continuation of this composition research with the purpose of subsequent introduction of the obtained medicine into medical practice.

References

- [1] Arslanov, M. M., Kamalov, I. I., & Fattakhov, V. V. (2011) Fizioterapevicheskie metody lecheniya khronicheskogo prostatita [Physiotherapy treatment of chronic prostatitis]. *Prakticheskaya medicina*, 1(49), 22–24. [in Russian].
- [2] Sharykina, N. I. (Ed) (2013) Derzhavnyi reiestr likarskykh zasobiv Ukrainy. Kyiv. Retrieved from <http://www.driz.kiev.ua>. [in Ukrainian].
- [3] Solihov, D. N. (2009) Vobenzim v lechenii khronicheskogo bakterial'nogo prostatita [Vobenzim and treatment of chronic prostatitis]. *Doklady akademii nauk Respubliki Tadjikistan*, 52(5), 400–402. [in Russian].
- [4] Bratchikov, O. I., Shestakov, S. G., Shumakova, E. A., & Makhov, S. V. (2008) The increase of clinico-immunological efficiency in complex therapy of patients with chronic prostatitis. *Urology*, 2, 44–49.
- [5] Al-Shukri, S. Kh., Petlenko, S. V., Borovets, S. Yu., Rybalov, M. A., Soroka, I. V., & Stukan', N. I. (2016) Effect of Prostatiene® AC and Prostatiene® on the ejaculate level of antisperm antibodies in the treatment of patients with chronic abacterial prostatitis and concomitant reproductive dysfunctions. *Andrology and genital surgery*, 1(17), 40–43. doi: <http://dx.doi.org/10.17650/2070-9781-2016-17-1-40-43>.
- [6] Tikhonov, A. I., Tikhonova, S. A., Yarnykh, T. G., Shpychak, O. S., et al. (2010) *Med natural'nyj v medicini i farmacii (proiskhozhdenie, svoystva, primeneniye, lekarstvennyye preparaty) [Honey natural in medicine and pharmacy (origin, properties, applications, medicinal products)]*. Kharkiv: Original. [in Russian].
- [7] Tichonov, A. I., Jamych, T. G., Czernych, W. P. et al. (2005) *Teoria i praktyka vytvarzania lecznykh preparatov propolisovych*. Kraków: Marka.
- [8] Tichonow, A. I., Sodzawiczny, K., Tichonowa, S. A., Jamych, T. G., Bondarczuk, L. I., & Kottenko, A. M. (2008) *Pylek kwiatowy obnoze pszczele w farmacji i medycynie. Teoria, technologia, zastosowanie lecznicze*. Kraków: Apipol-Pharma.
- [9] Shpychak, O. S. (2016) *Teoretychne ta eksperymentalne obhruntuvannia skladu i rozrobka tehnolohii likarskykh apipreparativ dlia zastosuvannia u sportyvni medytsyni*. (Avtoref. dis... dokt. farm. nauk) [Theoretical and experimental study of composition and development of medical technology apipreparativ for use in sports medicine Dr. farm. sci. diss.]. Kharkiv. [in Ukrainian].
- [10] Shpychak, O. S., Tykhonov, O. I., Zupanets, I. A., & Shebeko, S. K. (2015) The experimental study of the anti-inflammatory properties of combined aerosols with the propolis phenolic hydrophobic drug. *The Pharma Innovation*, 3(11), 26–29.
- [11] Shpychak, O. S., Tykhonov, O. I., Zupanets, I. A., Shebeko, S. K. (2015) The study of the analgesic properties of combined aerosols with the propolis phenolic hydrophobic drug in the experiment. *The Pharma Innovation*, 4(3), 78–81.
- [12] Spychak, O. S., Tykhonov, O. I., Kotov, A. H., et al. (2014) *Med [Honey]. Derzhavna farmakopeia Ukrainy*, (Vol. 2), (P. 436–439). Kharkiv: Derzhavne pidpriemstvo «Ukrainskyi naukovyi farmakopeinyi tsentr yakosti likarskykh zasobiv» [in Ukrainian].
- [13] Tykhonov, O. I., Yudin, O. I., Yarnykh, T. H., Shpychak, O. S., et al. (2015) TUU 10.8–39834691–001:2015 Med poroshkopodibny [Powdered honey]. Kyiv. [in Ukrainian].
- [14] Yudin, O. I. (2010) Innovacionnye tekhnologii i konstruktivnye osobennosti oborudovaniya dlia polucheniya pishevykh poroshkov [Innovative technologies and design features of equipment for obtaining food powders]. Kharkiv. [in Russian].
- [15] Stefanov, O. V. (Ed) (2001) *Doklinichni doslidzhennia likarskykh zasobiv [Preclinical studies of drugs]*. Kyiv: Avitsenna. [in Ukrainian].
- [16] Yakovleva, L. V. (1992) *Poisk i izuchenie novykh NPVP – proizvodnykh dikarbonovykh kislot (Dis... dokt. farm. nauk) [Search and study of new NSAID – derivatives of dicarboxylic acids. Dr. farm. sci. diss.]* Kharkiv. [in Russian].
- [17] Kovalenko, V. N. (Ed) (2017) *Kompendium 2015 – lekarstvennyye preparaty [Compendium 2016 – medicines]*. Kyiv: MORION. [in Russian].
- [18] Karateev, A. E., Uspensky, Yu. P., Pakhomova, I. G., & Nasonov, E. L. (2012) *Kratkij kurs istorii NPVP [A concise course of the history of NSAIDs]. Nauchno-prakticheskaya revmatologiya*, 3(52), 101–106. [in Russian].
- [19] Zaharevskij, A. S. (1962) *Vliyaniye nekotorykh proizvodnykh indola na nervnyy sistem (Dis...kand. med. nauk) [Influence of some indole derivatives on the nervous system. Dr. med. sci. diss. Minsk]*. [in Russian].
- [20] Shpychak, O. S., & Tikhonov, O. I. (2014) Eksperymentalne doslidzhennia spetsyficnoi farmakolohichnoi dii kombinovanoho heliu «Artproment» [The experimental study of the specific pharmacological action of «Artproment®» combined gel]. *Zaporozhye medical journal*, 4(85), 103–106. [in Ukrainian].
- [21] Lar'yanovskaya, Yu. B., Dranova, I. N., Kishinec, N. V., Dzyuba, I. P., & Butenko, I. G. (1999) *Holodovaya travma predstatel'noj zhelezy krysy kak e'ksperimental'naya model' prostatita [Cold injury of the prostate gland of the rat as an experimental model of prostatitis]. Proceedings of the V National Congress of Pharmacists of Ukraine*. Kharkiv: Prapor. [in Russian].
- [22] Bomko, T. V., Maslova, N. F., Kozlova, N. G., Dolgaya, I. N., & Pyatikop, A. B. (2002) *Farmakologicheskoe izuchenie suppozitoriev s maslom semyan tykvy na modeli e'ksperimental'nogo prostatita [Pharmacological study of suppositories with pumpkin seed oil on the model of experimental prostatitis]. Visnyk farmatsii*, 2(30), 90–92. [in Russian].
- [23] Gus'kov, A. R. (2008) *Istoki khronicheskogo prostatita [The origins of chronic prostatitis]*. Moscow: Medica. [in Russian].
- [24] Bent, H. H. (2002) The biochemistry and medical significance of the flavonoids. *Pharmacology and Therapeutics*, 96(2–3), 167–202. doi: [10.1016/S0163-7258\(02\)00298-X](https://doi.org/10.1016/S0163-7258(02)00298-X).
- [25] Serov, V. V., & Paukov, V. S. (1995) *Vospalenie. Rukovodstvo dlya vrachej [Inflammation. Guidelines for doctors]*. Moscow: Medicina. [in Russian].

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