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THEORETICAL AND EXPERIMENTAL JUSTIFICATION OF DEVELOPMENT OF DERMATOLOGICAL MEDICINAL PRODUCTS BASED ON NATURAL COMPOUNDS OF NAFTALAN OIL

Rationale. *In the article, data from domestic and foreign literature sources regarding the feasibility of developing new dermatological medicinal products based on natural compounds of Naftalan oil, particularly with refined Naftalan oil, was analyzed. The results of original experimental screening studies on the anti-inflammatory and analgesic effects of test samples containing natural substances from petroleum products, using the carrageenan-induced edema model in rats, are presented.*

The aim of the study *– Summarization of theoretical foundations for development of improved dermatological medicinal products and experimental pharmacological study of new soft dosage forms with varying compositions of active pharmaceutical ingredients (petroleum products) and excipients.*

Research materials and methods. *In this study, we conducted a bibliosemantic analysis of current data regarding properties of Naftalan oil and refined Naftalan oil, their differences, and potential advantages. The results of original screening studies of soft dosage forms containing petroleum products were presented. Experimental test samples with varying quantitative compositions of active pharmaceutical ingredients (Naftalan oil, refined Naftalan oil, mineral oil) and excipients were subjected to pharmacological investigation. The anti-inflammatory and analgesic activities of the test samples were evaluated using a standardized model of carrageenan-induced edema in laboratory rats*

Research results and discussion. *The investigated test samples containing natural substances from petroleum products exhibited a weak dose-dependent anti-inflammatory activity, which was more pronounced in test samples with a hydrophilic cream base compared to samples with similar composition on a hydrophobic ointment base. The highest anti-inflammatory activity (23.0%) was demonstrated by test sample № 3, which contained 10% refined Naftalan oil on a hydrophilic cream base. Test samples developed on a hydrophobic ointment base showed more potent analgesic activity. High levels of analgesic activity were demonstrated by test sample № 7 (98.3%), test sample № 6 (87.2%), test sample № 9 (70.9%), and test sample № 8 (42.5%). We believe that analgesic activity of test samples*

was exerted due to salicylic acid, the active ingredient with keratoplastic action, which was added to ointments at a concentration of 3% w/w.

Conclusions. *Theoretical foundations of potential therapeutic properties of new soft dosage forms based on natural substances with petroleum products proved to be somewhat different from the results of our experimental research. The obtained pharmacological study data indicates the presence of a rather weak anti-inflammatory activity in natural substances with petroleum products on a hydrophilic cream base. In test samples on a hydrophobic ointment base, this activity is practically absent. However, analgesic activity was more pronounced in all test samples, and was the highest in dosage forms on a hydrophobic ointment base, which is likely due to salicylic acid. In our opinion, the greatest prospects are opening up for refined Naftalan oil, but most likely as an excipient for the development of new dermatological medicinal products. The optimal concentration of refined Naftalan oil in soft dosage forms should be considered in the range of 10% to 15%.*

Key words: *petroleum products, Naftalan, Naftalan oil, refined Naftalan oil, anti-inflammatory activity, analgesic activity, screening pharmacological studies.*

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ТЕОРЕТИЧНЕ Й ЕКСПЕРИМЕНТАЛЬНЕ ОБҐРУНТУВАННЯ РОЗРОБЛЕННЯ ДЕРМАТОЛОГІЧНИХ ЛІКАРСЬКИХ ЗАСОБІВ НА ОСНОВІ ПРИРОДНИХ СПОЛУК НАФТАЛАНСЬКОЇ НАФТИ

Актуальність. *У статті аналізуються дані джерел вітчизняної й зарубіжної літератури щодо доцільності розроблення нових дерматологічних лікарських засобів на основі природних сполук нафталанської нафти, зокрема з очищеним нафталановим маслом. Наведено результати власних експериментальних скринінгових досліджень протизапальної та аналгетичної дії тест-зразків природних субстанцій із нафтопродуктів на моделі карагінанового набряку у щурів.*

Мета дослідження *– узагальнення теоретичних засад розроблення вдосконалених дерматологічних лікарських засобів та експериментальне фармакологічне дослідження нових м'яких лікарських засобів із різним складом активних фармацевтичних інгредієнтів (нафтопродуктів) і допоміжних речовин.*

Матеріал і методи. *У дослідженні проведено бібліосемантичний аналіз сучасних даних щодо властивостей нафталанської нафти та очищеного нафталанового масла, їхніх відмінностей і потенційних переваг. Наведено результати власних*

скринінгових досліджень м'яких лікарських засобів із нафтопродуктами. Експериментальні тест-зразки з різним кількісним складом активних фармацевтичних інгредієнтів (нафталанської нафти, очищеного нафталанового масла, вазелінового масла) і допоміжних речовин піддавалися фармакологічному дослідженню. Протизапальну та аналгетичну активність тест-зразків проводили на стандартизованій моделі карагінан-індукованого набряку у лабораторних щурів.

Результати дослідження. *У досліджуваних тест-зразків, які містили природні субстанції з нафтопродуктів, виявлено слабку дозозалежну протизапальну активність, що була більш виражена у тест-зразків на гідрофільній кремовій основі, ніж в аналогічних за складом зразках на гідрофобній мазевій основі. Найвищий показник протизапальної активності (23,0%) продемонстрував тест-зразок № 3, який містив очищене нафталанове масло 10% на гідрофільній кремовій основі. За аналгетичною активністю переваги мали тест-зразки, розроблені на гідрофобній мазевій основі. Високі показники аналгетичної активності продемонстрували: тест-зразок № 7 (98,3%); тест-зразок № 6 (87,2%); тест-зразок № 9 (70,9%); тест-зразок № 8 (42,5%). Уважаємо, що аналгетична активність зумовлена діючою речовиною кератопластичної дії – саліциловою кислотою, яку вводили до складу мазей у концентрації 3% м/м.*

Висновок. *Теоретичні засади щодо потенційних лікувальних властивостей нових м'яких лікарських засобів на основі природних субстанцій із нафтопродуктами виявилися дещо інакшими, ніж результати експериментального дослідження. Отримані дані фармакологічного вивчення свідчать про наявність доволі слабкої протизапальної активності у природних субстанцій із нафтопродуктів на гідрофільній кремовій основі. У тест-зразків на гідрофобній мазевій основі ця активність практично відсутня. Проте аналгетична активність була більш виражена в усіх тест-зразках, але найвище у лікарських формах на гідрофобній мазевій основі, що, напевно, зумовлено саліциловою кислотою. Найбільші перспективи, на нашу думку, відкриваються у очищеного нафталанового масла, але, скоріше за все, як допоміжної речовини для розроблення нових дерматологічних лікарських засобів. Оптимальною концентрацією очищеного нафталанового масла в м'яких лікарських засобах слід уважати від 10% до 15%.*

Ключові слова: *нафтопродукти, нафталан, нафталанська нафта, очищене нафталанове масло, протизапальна активність, аналгетична активність, скринінгові фармакологічні дослідження.*

Introduction. Rationale. In recent years, there has been growing attention from scientists and practicing physicians towards medicinal products of natural origin. This is due to the attractive safety profile of such medicines, their broad spectrum of therapeutic action, many years of successful use in clinical practice, and popularity among patients.

Substances of natural origin include Naftalan oil (so-called "black Naftalan oil"), Naftalan – an ointment derived from Naftalan oil (currently unavailable on Ukrainian pharmaceutical market), and vaseline oil.

Naftalan oil is a unique natural substance that has been used for over two hundred years to treat various pathological conditions and skin diseases. Naftalan oil was first obtained in the village of Safi-Kyurd, located near the city of Naftalan in Azerbaijan, in the 11th-12th centuries (Adigozalova et al., 2017). For a long time, residents of Safi-Kyurd and surrounding cities used Naftalan oil to treat various skin diseases such as eczema, psoriasis, burns, and others. In the 13th century, Italian traveler Marco Polo reported of Naftalan oil and its properties. In 1890, German engineer E. Jager noticed successful treatment of various diseases with this oil and began constructing a factory near the oil extraction source to produce "Naftalan" ointment, which was successfully sold in pharmacies in London, Hamburg, Tokyo, and Cairo. This ointment was also used by military medics to treat gunshot wounds, burns, and frostbite (Kravchenko & Kiaziamov, 2006). Naftalan ointment was widely used by doctors; later, cosmetologists began using it to improve facial skin condition in various diseases (Isayeva, 2023).

Naftalan oil (NO) is a thick syrupy substance, brown in color, with a pleasant smell, almost indistinguishable in appearance from other types of oil and similar to heavy resinous oils (Gulieva, S. A., 1981). NO contains a plethora of various hydrocarbons, among which naphthenic (50% to 60%) and aromatic (31%). It also contains resins (14%), naphthenic acids (0.5% to 1%), nitrogenous bases (up to 0.3%), and water 10–15% (Adigozalova, 2016).

Over the past 100 years, intensive scientific study has been conducted, alongside widespread medical use of soft dosage forms with NO for treatment of dermatological diseases. To produce medicines, a Naftalan substance is obtained from NO. Along with positive clinical results obtained during the clinical use of ointments with NO, some pharmaceutical issues remained unresolved, including unpleasant odor, coloring properties, and difficulty in combining with some active pharmaceutical ingredients (APIs). The main problem was the lack of data on the exact composition and standardization of substances from NO, particularly, the distribution of polycyclic aromatic hydrocarbons, their major and minor components (fractions of naphthenic hydrocarbons), which is crucial for understanding of mechanisms of action, therapeutic effects, and possible adverse reactions.

Polycyclic aromatic hydrocarbons (PAHs) are organic compounds characterized by the presence of two or more condensed benzene rings in their chemical structure. Since Naftalan substance is a product of NO processing that may contain a significant amount of PAHs, their content in the Naftalan substance for pharmaceutical purposes should be limited. The type of impact of PAHs on living biological systems mainly depends on the structure of hydrocarbons and can vary widely. Many PAHs are strong chemical carcinogens. For example,

compounds like benz[a]anthracene, benzopyrene, and ovalene have pronounced carcinogenic, mutagenic, and teratogenic properties.

According to the EU regulatory document No. 1223/2009 (Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products), the amount of polycyclic aromatic hydrocarbons extracted with dimethyl sulfoxide from petroleum extracts used for the production of cosmetic products is regulated at a level of not more than 3.0% (by naphthalene). This criterion characterizes the toxicity limit of petroleum products, as their toxicity is determined by the content of PAHs. Therefore, for petroleum products, instead of long-term toxicity studies at the initial stages of experimental research, PAH content is being determined.

The upper limit of 3.0% for PAH content is significantly higher than the acceptability criterion for the content of polycyclic aromatic hydrocarbons established in the monographs of State Pharmacopoeia of Ukraine (SPU). According to the SPU monograph "Petrolatum", polycyclic aromatic hydrocarbons contents in the petrolatum substance should not exceed 0.03%. Therefore, for the Naftalan substance, it is suggested to limit contents of polycyclic aromatic hydrocarbons to the level of their limitation in petrolatum, namely, to 0.03%.

A new page in the history of officinal dosage forms with NO was opened when refined Naftalan oil (RNO) was obtained. Unlike unrefined NO, or the so-called "black Naftalan oil", RNO is the result of deeper processing of NO, formed after removal of potentially carcinogenic and allergenic fractions of petroleum hydrocarbons. It is devoid of coloring and unpleasant organoleptic properties, and its technological properties are significantly improved.

Results of successful clinical application of ointments with NO contributed to an in-depth study of its pharmacodynamics, while its drawbacks prompted scientists and clinical researchers to improve dermatological dosage forms by replacing Naftalan with RNO to enhance their biopharmaceutical properties, strengthen pharmacological action, and enable combination with various APIs and excipients. The aforementioned theoretical prerequisites became the fundamental basis for development and subsequent screening research of new dosage forms with RNO, implemented within the framework of this research.

The aim of the study was to examine theoretical foundations for development of improved dermatological medicinal products and conduct experimental pharmacological research on new soft dosage forms with varying compositions of active pharmaceutical ingredients (petroleum products) and excipients.

Research materials and methods. We investigated test samples that differed in qualitative composition (i.e., the presence of refined or unrefined Naftalan oil), quantitative content of NO or RNO, type of a base (hydrophilic cream and hydrophobic ointment) and composition of excipients; some test samples contained 3% salicylic acid in their ointment bases. The composition of investigated test samples is presented in table 1. Preparations on hydrophilic and hydrophobic bases are necessary for various dermatological diseases and different phases of certain diseases.

Refined Naftalan oil (RNO) is a natural substance of organic origin, a highly purified fraction of Naftalan oil (NO), a transparent substance with a mild characteristic odor, containing naphthenic hydrocarbons. According to various researchers, it exhibits analgesic, anti-inflammatory, desensitizing, angioprotective, and

Table 1

The composition of investigated test samples of soft dosage forms with petroleum product substances

Test sample, code	Content of substances in test samples, showed in %					Base of a test sample
	Refined Naftalan oil	Naftalan oil	Vaseline oil	Salicylic acid	Hydrocortisone acetate	
TS* № 1	-	-	10,0	-	-	Hydrophilic
TS № 2	-	10,0	-	-	-	Hydrophilic
TS № 3	10,0	-	-	-	-	Hydrophilic
TS № 4	15,0	-	-	-	-	Hydrophilic
TS № 5	-	-	-	-	1,0	Hydrophilic
TS № 6	-	-	15,0	3,0	-	Hydrophobic
TS № 7	-	10,0	-	3,0	-	Hydrophobic
TS № 8	10,0	-	-	3,0	-	Hydrophobic
TS № 9	15,0	-	-	3,0	-	Hydrophobic
TS № 10	-	-	-	-	1,0	Hydrophobic

* TS – test sample

antipruritic effects. Isolated studies shown that RNO stimulated regenerative processes and suppressed inflammatory processes in the setting of dermatological diseases, accelerated regression of pathological manifestations, and promoted resorption of psoriatic skin lesions (Shmyhlo et al., 2004).

To theoretically justify development of new medicinal products with NO and RNO, we employed general theoretical scientific approaches, including the method of bibliosemantic analysis, information synthesis, and generalization. The experimental pharmacological study of anti-inflammatory and analgesic effects of test samples was conducted using the carrageenan-induced edema model in rats (Stefanov O.V., 2001). The anti-inflammatory action was evaluated in 2 and 4 hours after carrageenan-induced inflammation. The anti-edema effect, as an indicator of anti-inflammatory activity, was assessed by measuring the change of the rat paw volume, when injected with carrageenan, compared to the control group over the same observation period. The rat paw volume (in conventional units) was recorded using a Ugo Basile plethysmometer (Italy). Analgesic activity was assessed by measuring changes in the pain threshold (PT) in animals using the "tail flick" test with a Ugo Basile analgesiometer (Italy), by stimulating the proximal part of the tail with a focused infrared beam and subsequently forming groups of animals with initial PT values ranging from 4 to 12 seconds (Seredynska, 2014; McMahon et al, 2021).

Statistical processing of the obtained data was performed by determining the normality of distribution, which was assessed using the Shapiro-Wilk test (W). The obtained values followed a normal distribution. Data are presented as arithmetic means and standard errors of the mean. The significance of a difference between mean values in two samples was determined using the Student's t-test. Differences were considered statistically significant at a significance level of at least 95% ($p<0,05$).

All studies were conducted in accordance with the rules and norms of humane treatment of animals in experimental research (Council of Europe, 1986) and certified by the Expert Opinion of the Bioethics Commission of Bogomolets National Medical University.

Research results and discussion. The results obtained over the course of the screening study of the pharmacological action of test samples of soft dosage forms with varying concentrations of RNO are shown in table 2.

The evaluation of anti-edema effect indicates a weak anti-inflammatory activity (AIA) in the investigated test samples. The highest AIA was demonstrated by test sample № 3, which contained 10% RNO on a hydrophilic cream base. Test sample № 1 (10% vaseline oil on a hydrophilic cream base) showed half the anti-inflammatory activity, at 12.8%; test sample № 2, containing 10% Naftalan oil on a hydrophilic cream base, demonstrated an anti-inflammatory activity of 8.3%; test sample № 5 (comparator on a hydrophilic cream base), containing 1% hydrocortisone acetate on a hydrophilic cream base, showed only 10.9% anti-inflammatory effect. Meanwhile, test sample № 10, containing 1% hydrocortisone acetate on a hydrophobic ointment base (comparator on a hydrophobic ointment base) exhibited significantly lower anti-inflammatory activity, equal to 3.2%.

Table 2

Results of the study on anti-inflammatory and analgesic effects of test samples of soft dosage forms with petroleum product substances using the carrageenan-induced edema model in rats

Experimental animal groups	Observation period, 2 hours	
	Pharmacological activity, %	
	Anti-inflammatory activity	Analgesic activity
Test sample № 1 – 10% vaseline oil, hydrophilic base, cream (n=14)	12.8	19.3
Test sample № 2 – 10% Naftalan oil, hydrophilic base, cream (n=14)	8.3	4.9
Test sample № 3 – 10% refined Naftalan oil, hydrophilic base, cream (n=9)	23.0	-3.9
Test sample № 4 – 15% refined Naftalan oil, hydrophilic base, cream (n=9)	8.9	– 8.5
Test sample № 5 – 1.0% hydrocortisone acetate cream (comparator on hydrophilic base) (n=14)	10.9	23.4
Test sample № 6 – 15% vaseline oil, hydrophobic base, ointment (n=9)	3.9	87.2
Test sample № 7 – 10% Naftalan oil, hydrophobic base, ointment (n=9)	8.9	98.3
Test sample № 8 – 10% refined Naftalan oil, hydrophobic base, ointment (n=9)	1.9	42.5
Test sample № 9 – 15% refined Naftalan oil, hydrophobic base, ointment (n=9)	6.4	70.9
Test sample № 10 – 1.0% hydrocortisone acetate ointment (comparator on hydrophobic base) (n=9)	3.2	2.8

All other test samples on the hydrophobic ointment base, except for the one composed of 10% Naftalan oil on a hydrophobic base (test sample № 7), showed anti-inflammatory activity ranging from 1.9% to 6.4%. Test sample № 7 demonstrated an anti-inflammatory activity of 8.9%.

Test sample № 9, containing 15% RNO but on a hydrophobic ointment base, despite a 50% increase in RNO compared to test sample № 8 (containing 10% RNO on a hydrophobic ointment base), showed only slightly higher anti-inflammatory activity of 6.4% versus 1.9% in test sample № 8.

Test sample № 10 (comparator), containing 1% hydrocortisone acetate but on a hydrophobic ointment base, demonstrated an anti-inflammatory effect of 3.2%, which is 3 times less than 1% hydrocortisone acetate on a hydrophilic cream base (test sample № 5).

Thus, the investigated soft dosage forms containing natural substances from petroleum products exhibited weak dose-dependent anti-inflammatory activity, which was more pronounced in test samples on a hydrophilic cream base than in samples with similar composition on a hydrophobic ointment base. Hydrocortisone acetate 1%, as a hydrophilic substance in a hydrophilic base, naturally showed three times greater anti-inflammatory activity than the same concentration of hydrocortisone acetate 1% on a hydrophobic ointment base, while still being more than twice less effective than 10% RNO on a hydrophilic cream base (test sample № 3). This means that an anti-inflammatory effect of our investigated test sample with 10% RNO was higher that the one for a corticosteroid – 1% hydrocortisone, but only on a hydrophilic cream base. Therefore, this sample might be promising for further in-depth study on a model of skin pathology, such as psoriasis.

Regarding analgesic activity, which was more pronounced, test samples № 7, № 6, № 9, and № 8, developed on a hydrophobic ointment base, showed advantages. They demonstrated high levels of analgesic activity: 98.3% (test sample № 7); 87.2% (test sample № 6); 70.9% (test sample № 9); 42.5% (test sample № 8) respectively. Analgesic activity was explained by presence of salicylic acid. Since the contents of salicylic acid is constant and is at 3% in each sample, the variation in analgesic effect is explained by different contents of excipients and the amount of RNO. Thus, the sample containing 15% RNO showed a greater analgesic effect than the sample with 10% RNO.

The comparator 1% hydrocortisone acetate on a hydrophobic ointment base showed practically no analgesic activity, with its indicator equal to 2.8%. Meanwhile, 1% hydrocortisone acetate on a hydrophilic cream base (test sample № 5) demonstrated an analgesic activity of 23.4%, which is almost 9 times higher. Test sample № 1, containing 10% vaseline oil on a hydrophilic cream base, showed weak analgesic activity of 19.3%, lower than the test samples of petroleum products on hydrophobic ointment bases. Test sample № 2 showed the lowest analgesic activity at 4.9%. Interestingly, data for test samples № 3 and №4 with RNO showed, on the contrary, a decrease in the pain threshold (PT). At a concentration of 10% RNO on a hydrophilic cream base, it decreased PT by 3.9%, while increasing the concentration to 15% raised PT by 8.5%. This can probably be explained by differences in the composition of excipients that increase sensitivity of nerve endings to nociceptive stimuli.

High analgesic activity (98.3%) of test sample № 7, containing 10% Naftalan oil (unrefined, with a higher content of PAHs and other naphthenic hydrocarbons), is noteworthy. This is probably explained by the higher content of substances that contribute to increasing the analgesic effect of salicylic acid.

Conclusions

Theoretical analysis of current scientific data indicates a certain therapeutic potential of topical medicinal products containing petroleum products, namely Naftalan oil, vaseline oil, and refined Naftalan oil, particularly in the setting of dermatological diseases. However, our experimental studies demonstrated that the investigated pharmaceutical ingredients from petroleum products exhibit rather weak anti-inflammatory activity, and only in combination with a hydrophilic cream base, while this activity was almost completely lost on a hydrophobic ointment base. Nevertheless, the emergence of analgesic activity, which was more pronounced in test samples on a hydrophobic ointment base, can be explained by the presence of salicylic acid. The absence of anti-inflammatory effects in test samples on a hydrophobic ointment base can only be explained by the fact that the change to a hydrophobic ointment base and a different spectrum of excipients used for this dosage form do not allow salicylic acid to exhibit its anti-inflammatory properties. Salicylic acid belongs to non-steroidal anti-inflammatory drugs, which are significantly less potent than diclofenac, ketoprofen, and other medicinal products in this group. Therefore, the low concentration of 3% salicylic acid may explain the lack of anti-inflammatory activity in test samples on a hydrophobic ointment base that contained it. As is known, at low concentrations, salicylic acid exhibits not so much anti-inflammatory as keratolytic and keratoplastic types of action. This may justify its

inclusion in dermatological products for the treatment of diseases accompanied by hyperkeratosis, such as psoriasis.

Results of our screening study open up prospects for using refined Naftalan oil as a new excipient in combination with active pharmaceutical ingredients that demonstrate proven anti-inflammatory action. The optimal content of refined Naftalan oil should be considered 10% as an excipient in such dosage forms. For the purpose of developing dermatological medicinal products that may exhibit analgesic action, the most promising is 15% refined Naftalan oil, particularly on a hydrophobic ointment base, since it is in this concentration and in combination with salicylic acid, that its greatest analgesic activity is manifested.

However, refined Naftalan oil has a favorable safety profile, improved pharmaceutical properties, and can exhibit synergistic activity in combination with anti-inflammatory and other active pharmaceutical ingredients. This opens up prospects for further experimental studies.

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Gorchakova N.O. – data collection and analysis, article writing, article correction;
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