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The study of the antimicrobial activity of a new anhydrous gel “Hypericum-derma” for the treatment of purulent wounds

Aim. To determine the phytochemical composition and study the antimicrobial activity of a new anhydrous gel “Hypericum-Derm” for the treatment purulent wounds.

Materials and methods. The study objects were the anhydrous gel “Hypericum-Derm” containing α-arbutin, clotrimazole, lidocaine hydrochloride, the *Hypericum perforatum* herb extract, the *Crataegus monogyna* leaf and flower extract. The quantitative determination of the main biologically active compounds was performed by spectrophotometric and titrimetric method of analysis; the antimicrobial effect was assessed using the agar well diffusion method and the minimum inhibition concentration (MIC).

Results. The total content of polyphenols was 0.45 %, flavonoids – 0.35 %, organic acids – 0.16 %, hydroxycinnamic acid derivatives – 0.20 % and anthracene derivatives – 0.02 % in the anhydrous gel “Hypericum-Derm”. The experimental studies showed that the anhydrous gel “Hypericum-Derm” was active against strains of *Pseudomonas aeruginosa* (25.0 mm), *Proteus vulgaris* (25.0 mm), *Escherichia coli* (25.0 mm), *Staphylococcus aureus* (26.0 mm), *Bacillus subtilis* (25.0 mm) and *Candida albicans* (23.0 mm). The MIC values of the “Hypericum-Derm” gel was 0.018 mg/mL against *S. aureus* and *B. subtillis*, 0.035 mg/mL against *P. aeruginosa, P. vulgaris, E. coli* and *C. albicans*, which was 10 times lower than the MIC values of the reference drug “Levomekol”.

Conclusions. The phytochemical composition of the anhydrous gel “Hypericum-Derm” has been determined: phenolic compounds and flavonoids dominate in the gel, while anthracene derivatives have been found in the smallest amount. The anhydrous gel “Hypericum-Derm” has shown a high antimicrobial effect against Gram-positive and Gram-negative bacteria, and fungi. Thus, the anhydrous gel “Hypericum-Derm” can be used to treat purulent-necrotic wounds.

***Key words**: purulent wound; gel; St. John’s wort; hawthorn; phenolic profile.*

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Дослідження антимікробної активності нового безводного гелю «Гіперікум-дерм» для лікування гнійних ран

Метою дослідження було визначення фітохімічного складу та дослідження антимікробної активності нового безводного гелю «Гіперікум-Дерм» для лікування гнійних ран.

Матеріали та методи. Об’єктом дослідження був безводний гель «Гіперікум-Дерм», до складу якого входить α-арбутин, клотримазол, лідокаїну гідрохлорид, екстракт трави звіробою звичайного, екстракт листя та квіток глоду одноплідного. Кількісне визначення основних біологічно активних сполук проводили спектрофотометричним та титрометричним методами аналізу; антимікробний ефект оцінювали з допомогою методу дифузії в агарі в модифікації «колодязів» та мінімальної інгібувальної концентрації (МІК).

Результати та їхнє обговорення. Загальний вміст поліфенолів становив 0,45 %, флавоноїдів – 0,35 %, органічних кислот – 0,16 %, похідних гідроксикориних кислот – 0,20 % та антраценпохідних – 0,02 % у безводному гелі «Гіперікум-Дерм». Експериментальні дослідження показали, що безводний гель «Гіперікум-Дерм» активний проти штамів *Pseudomonas aeruginosa* (25,0 мм), *Proteus vulgaris* (25,0 мм), *Escherichia coli* (25,0 мм), *Staphylococcus aureus* (26,0 мм), *Bacillus subtilis* (25,0 мм) та *Candida albicans* (23,0 мм). Значення МІК гелю «Гіперікум-Дерм» становило 0,018 мг/мл проти *S. aureus* та *B. subtillis*, 0,035 мг/мл проти *P. aeruginosa*, *P. vulgaris*, *E. coli* та *C. albicans*, що було в 10 разів нижче за значення МІК препарату-стандарту «Левомеколь».

Висновки. Було встановлено фітохімічний склад безводного гелю «Гіперікум-Дерм», у складі якого домінують фенольні сполуки та флавоноїди, тоді як похідні антрацену виявлені в найменшій кількості. Безводний гель «Гіперікум-Дерм» виявив високу антимікробну дію проти грампозитивних та грамнегативних бактерій, грибів. Отже, безводний гель «Гіперікум-Дерм» може бути використаний для лікування гнійно-некротичних ран.

***Ключові слова**: гнійна рана; гель; звіробій; глід; фенольний профіль.*

Introduction. The armed confrontation in the area the anti-terrorist operation/Joint Forces Operation, which began in 2014 and transformed into a war on February 24, 2022, continues to this day. According to data provided by the Office of the UN High Commissioner for Human Rights, more than 40 thousand people became victims of the military conflict from April 2014 to the end of 2020. people, more than 4 thousand military personnel were killed, more than 12 thousand were injured [1]. There is a clear gradation in the types of injuries: up to 60 % are mine-explosive, 20-22 % are combined, 10-13 % are burns. These data indicate the relevance of the problem of the wound and burn treatment for the healthcare system, both in the civil and military spheres, as general state tasks [2].

In modern literature, a wound is defined as a violation of the integrity of the skin or mucous membranes caused by mechanical action and usually accompanied by damage to deeper tissues or organs [3]. During the wound healing process, three phases are usually distinguished: Phase I is the inflammatory phase characterized by the release of necrotic tissue and foreign bodies from the wound; Phase II is the proliferation or regeneration phase; Phase III is the maturation or remodeling phase characterized by the wound closure and final scar formation [4].

At the Department of General Chemistry of the National University of Pharmacy (NUPh), teaching assistants Maslov O. Yu. and Komisarenko M. A. under the supervision of Professor Kolisnyk S. V. developed an anhydrous gel "Hypericum-Derm" consisting of α-arbutin (0.05 %), clotrimazole (0.005 %), lidocaine hydrochloride (2.0 %), the St. John's wort (*Hypericum perforatum*) herb extract (4.0 % by dry residue) and the hawthorn (*Crataegus monogyna*) leaf and flower extract (3.0 % by dry residue). The anhydrous gel was obtained based on "Levomekol" technologies; polyethyleneglycol 400:1500 (8:2) was chosen as the base for the anhydrous gel since at the first phase of the wound it was necessary to clean the wound from necrotic tissues and reduce the inflammatory reaction. This task is easily solved using a PEG base due to its high osmotic strength (336 %) [5].

The next key issue is the composition of combinations of active pharmaceutical ingredients that will have an antimicrobial effect against bacteria and fungi, as well as help to suppress inflammation and inactivate free radicals. To solve this problem, we turned to the experience of Soviet pharmacists; in the 60s of the 20-th century, the drug "Novoimanin" was developed and introduced in the USSR [6]. This drug was used as a solution for the treatment of burns, purulent-inflammatory diseases of wounds infected with Gram-positive strains. The active component of "Novoimanin" is the extract of St. John's wort, the main biologically active substances of the extract are flavonoid derivatives (rutin, hyperoside, quercetin), and anthracene derivatives (hypericin). Many studies have described that the St. John's wort extract has anti-inflammatory, antimicrobial, antioxidant, anticancer and analgesic effects [7], therefore, this extract is a suitable component for creating an anhydrous gel. Since we had the task to obtain an anhydrous gel that could inhibit "superbugs", we selected an important component, such as α-arbutin, to solve this problem. In our earlier works [8, 9], it was shown that α-arbutin promoted the active inhibition of the biofilm formation mechanism in resistant bacteria, such as AHS LasI responsible for the biofilm formation signaling system.

To prevent the formation of a polymicrobial biofilm between bacteria and fungi, we selected an antifungal drug "Clotrimazole". Polymicrobial biofilm is the main cause for non-healing in chronic wounds, especially in burns. To prevent the occurrence of symbiosis between bacteria and fungi, an antifungal agent should be used together with the prescribed therapy of broad-spectrum antibacterial drugs.

To enhance the anti-inflammatory and antioxidant activity, we included the hawthorn leaf and flower extract in the composition since the extract contained such active compounds as vitexin and isovitexin. Available studies published in journals indexed in Scopus and Web of Science have shown that these compounds have high cardioprotective, antimicrobial, wound-healing, anti-inflammatory, antioxidant, and neuroprotective effects [10].

The last and important component of our anhydrous gel is lidocaine hydrochloride. This component plays not only the role of a local anesthetic, but primarily as a compound that will suppress and prevent the bacterial film formation [11].

Thus, the aim of our work was to determine the phytochemical composition and study the antimicrobial activity of a novel anhydrous gel "Hypericum-Derm" for the treatment purulent wounds.

Materials and methods. The *Hypericum perforatum* (*H. perforatum*) herb and *Crataegus monogyna* (C. monogyna) leaves and flowers was the object of the study. They were collected in the places of their cultivation. The *H. perforatum* herb was collected in 2022 during the flowering period in July, whereas *C. monogyna* leaves and flowers were collected in 2023 during the flowering period in May in the vicinity of the village of Ternova, Kharkiv region (50°19′31″ N, 36°66′93″ E; the altitude above sea: 92 m).

25.0 g of the *H. perforatum* herb and *C. monogyna* leaves and flowers were ground to 1-2 mm in size. The extraction was carried out twice with 96 % ethanol in the ratio of 1/10 (*m/v*) of the raw material/solvent in a water bath at 80ºC with reflux for 1 hour. After cooling, the solutions were filtrated and concentrated to the raw material mass ratio of 1 to 1 using a rotary evaporator at 40 ºC under vacuum.

The total phenolic compounds were quantified using the Folin-Ciocaltau method, with absorbance readings taken at 760 nm [12]. The total content of flavonoids was found using the $AlCl_3$ assay where the absorbance was measured at 415 nm [12]. The total content of hydroxycinnamic acid derivatives was measured by the assay of complex formation with $NaNO_2$-Na_2MoO_4, the absorbance was measured at 505 nm [12]. The content of total organic acids was found through acid-base titration, using the potentiometric method to determine the

end-point [12]. The amount of anthracene derivatives was determined by the molecular absorption analysis [13], the absorbance was measured at 591 nm.

α-Arbutin (≥98.0 %); "Clotrimazole" (≥98.0 %); lidocaine hydrochloride (≥98.0 %); "Gentamycin" (≥98.0 %), "Fluconazole" (≥98.0 %) were provided by the pharmaceutical company "Astrapharm" Kyiv, Ukraine; and by the pharmaceutical company "Zdravopharm", Kharkiv, Ukraine. "Levomekol", the batch number LMK-03-250722-01-UA, was from PrAT Pharmaceutical Factory "Viola".

S. aureus ATCC 25923, E. coli ATCC 25922, B. subtilis ATCC 6538, C. albicans ATCC 885/653, P. vulgaris NTCS 4636, and P. aeruginosa ATCC 27853 were used in accordance with the established guidelines for evaluating the antimicrobial efficacy of pharmaceuticals.

The agar well diffusion method was used in our work [14, 15].

The minimum inhibitory concentration (MIC) is defined as the lowest concentration of an antibacterial agent that completely prevents bacterial growth. The MIC for various extracts was determined using the microbroth dilution method [16].

To obtain statistical results, the Statistica 10 program was used, the results were analyzed using one-way ANOVA with the Tukey's criterion. Differences were considered significant at $p<0.05$.

Results and discussion. According to the results obtained (Table 2), the anhydrous gel "Hypericum-Derm" (0.45±0.04 %) had a higher content of phenolic compounds than other biologically active compounds.

Table 2 demonstrates that the total content of flavonoids in the anhydrous gel "Hypericum-Derm" was 0.35±0.01 % calculated with reference to rutin and 0.17±0.01 % calculated with reference to vitexin. The percentage of flavonoids out of total polyphenols in the anhydrous gel "Hypericum-Derm was 78 % and 38 % calculated with reference to rutin and vitexin, respectively".

In the anhydrous gel "Hypericum-Derm", the total organic acids were 2.8 times lower than polyphenols, whereas in the *C. sinensis* leaf, the total organic acids were 6.3 times lower than polyphenols (Table 2).

Table 1

Criteria for interpreting the sensitivity of microorganisms

Microbial sensitivity	Diameter of the growth inhibition zone, mm
High sensitivity	>25
Sensitive	15-25
Low sensitivity	10-15
No sensitivity	<10

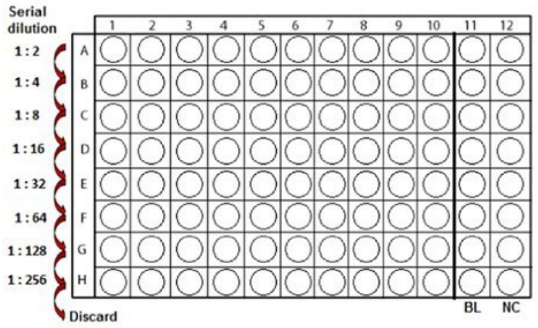

Figure 1. The serial dilution process in the microbroth dilution method

Table 2 demonstrates that the total content of hydroxycinnamic acid derivatives in the anhydrous gel "Hypericum-Derm" was 0.20±0.01 % calculated with reference to chlorogenic acid. The percentage of hydroxycinnamic acid derivatives out of total polyphenols was 44 % in the anhydrous gel "Hypericum-Derm".

According to the results in Table 2, the anhydrous gel "Hypericum-Derm" (0.02±0.001 %) had a lower content of anthracene derivatives than other biologically active compounds. The percentage of anthracene derivatives out of total polyphenols was 4 % in the gel "Hypericum-Derm".

The gel "Hypericum-Derm" had the greatest antibacterial effect. It demonstrated the inhibition effects against *P. aeruginosa* (25.0 mm), *P. vulgaris* (25.0 mm), *E. coli* (25.0 mm), *S. aureus* (26.0 mm), *B. subtilis* (25.0 mm) and *C. albicans* (23.0 mm). The antibacterial effect of the gel "Hypericum-Derm" was much higher than its own compounds: α-arbutin, clotrimazole, lidocaine

Table 2

The quantitative content of total phenolic compounds, flavonoids, hydroxycinnamic acid derivatives, anthracene derivatives and organic acids

Sample	Total phenolic content calculated with reference to gallic acid, %	Total anthracene derivatives calculated with reference to hyperecin, %	Total flavonoid content calculated with reference to rutin, %	Total flavonoid content calculated with reference to vitexin, %	Total content of hydroxycinnamic acid derivatives calculated with reference to chlorogenic acid, %	Total organic acids calculated with reference to citric acid, %
Anhydrous gel "Hypericum-Derm"	0.45±0.04	0.02±0.001	0.35±0.01	0.17±0.01	0.20±0.01	0.16±0.01

Notes: $n = 5$, $p < 0.05$.

hydrochloride, the *H. perforatum* herb and *C. monogyna* leaves and flowers. Moreover, this gel showed stronger antibacterial effects than the reference drug "Levomekol". The growth inhibition zones of the gel "Hypericum-Derm" was higher than those of the drug "Levomekol" in case of *P. aeruginosa*, *P. vulgaris, E. coli, S. aureus* and *B. subtilis* (Table 3).

No literature review has revealed any previous studies of the antibacterial effect of "Clotrimazole" on Gramm-negative and Gramm-positive resistant strains. "Clotrimazole" caused antibacterial effects on *P. aeruginosa*, *P. vulgaris*, *E. coli*, *S. aureus* and *B. subtilis* with the inhibition zones of 17.0, 17.0, 17.0, 18.0 and 18.0 mm, respectively (Table 3).

The *H. perforatum* herb and *C. monogyna* leaf and flower extracts had the inhibition effect on the colony growth against *P. aeruginosa* (18.0 and 21.0 mm), *P. vulgaris* (18.0 and 20.0 mm), *E. coli* (15.0 and 19.0 mm), *S. aureus* (18.0 and 21.0 mm), *B. subtilis* (18.0 and 21.0 mm) and *C. albicans* (16.0 and 18.0 mm) (Table 3).

The polyethyleneglycol base exhibited the antibacterial activity against *P. aeruginosa* (21.0 mm), *P. vulgaris* (17.0 mm), *E. coli* (19.0 mm), *S. aureus* (20.0 mm), *B. subtilis* (22.0 mm) and *C. albicans* (18.0 mm).

Lidocaine hydrochloride and "Clotrimazole" showed the same antibacterial effects against strains, except *C. albicans* and *E. coli*. The growth inhibition zones of lidocaine hydrochloride were 17.0 and 18.0 mm, whereas "Clotrimazole" had 21.0 and 17.0 mm against *C. albicans* and *E. coli,* respectively (Table 3).

The gel "Hypericum-Derm" under study significantly inhibit the bacterial and fungi strains with MIC. In the antimicrobial study previously conducted, the gel "Hypericum-Derm" was the most active independently of the strains tested. Table 4 shows that the gel "Hypericum-Derm" with the MIC value of 0.018 mg/mL was the most active against *S. aureus*, and *B. subtilis*, whereas in the case of *E. coli, P. vulgaris* and *P. aeruginosa* the MIC was equal to 0.035 mg/mL. If the MIC values are compared with "Levomekol", we can observe that the MIC values of the gel "Hypericum-Derm" were much higher than that of the reference drug "Levomekol". The MIC values of "Clotrimazole" was the lowest in the study.

The MIC values of extracts *H. perforatum* and *C. monogyna* were much lower than MIC values of the gel "Hypericum-Derm". α-arbutin had the highest MIC values – 0.21 mg/mL against *S. aureus* and *B. subtilis,* and 0.50 mg/mL against *P. vulgaris*, *P. aeruginosa*, and *C.albicans*. The MIC values of lidocaine hydrochloride was high – 0.16 mg/mL against *S. aureus*.

The results of studying the antimicrobial activity of the anhydrous gel "Hypericum-Derm" and its components have shown that they are highly active against strains of *P. aeruginosa, P. vulgaris, E. coli, S. aureus, B. subtilis* and *C. albicans*. According to the data obtained (Table 4), at first glance it can be said that the antimicrobial activity of the gel "Hypericum-Derm" does not differ much from the antimicrobial effect of the reference drug "Levomekol". But upon further research determining the MIC value of the samples under study, we found that "Levomekol" was 10 times inferior to the anhydrous gel "Hypericum-Derm" developed. We found the same pattern in the case of extracts of *H. perforatum* and *C. monogyna*. In our opinion, such a low MIC value

Table 3

The inhibition zone (mm) obtained as a result of screening the antimicrobial activity of the anhydrous gel "Hypericum-Derm", its components and the reference drugs: "Gentamycin", "Fluconazole", "Levomekol"

Sample	Concentration, %	Diameter of the growth inhibition zone, mm±SD					
		Gramm-positive		Gramm-negative			Fungi
		S. aureus ATCC 25923	*B. subtilis* ATCC 6633	*E. coli* ATCC 25922	*P. vulgaris* ATCC 4636	*P. aeruginosa* ATCC 27853	*C. albicans* ATCC 653/885
Anhydrous gel "Hypericum-Derm"	0.45[a]	26.0±0.1	25.0±0.1	25.0±0.1	25.0±0.1	25.0±0.1	23.0±0.1
Polyethyleneglycol base 400 and 1500 (8:2)	–	20.0±0.2	22.0±0.2	19.0±0.2	17.0±0.2	21.0±0.2	18.0±0.2
H. perforatum extract	0.20[a]	18.0±0.2	18.0±0.2	15.0±0.2	18.0±0.2	18.0±0.2	16.0±0.2
C. monogyna extract	0.25[a]	21.0±0.2	21.0±0.1	19.0±0.1	20.0±0.1	21.0±0.1	18.0±0.1
α-Arbutin	0.05	19.0±0.1	18.0±0.1	16.0±0.1	16.0±0.1	17.0±0.1	18.0±0.1
"Clotrimazole"	0.005	18.0±0.1	18.0±0.1	17.0±0.1	17.0±0.1	17.0±0.1	21.0±0.1
Lidocaine hydrochloride	2.0	18.0±0.2	18.0±0.2	18.0±0.2	17.0±0.2	17.0±0.2	17.0±0.2
"Levomekol"	4.80[b]	25.0±0.1	25.0±0.1	24.0±0.1	23.0±0.1	24.0±0.1	23.0±0.1
"Gentamycin"	0.60	22.0±0.2	24.0±0.2	25.3±0.3	25.0±0.2	25.6±0.1	12.0±0.1
"Fluconazole"	0.30	18.0±0.2	12.0±0.2	14.3±0.3	12.3±0.3	10.0±0.2	20.0±0.1

Notes: a – the concentration of total phenolic compounds calculated with reference to gallic acid; b – the total concentration (4.0 % of methyluracil and 0.8 % of chloramphenicol.

Table 4

The minimal inhibitory concentration of the anhydrous gel "Hypericum-Derm", its components and the reference drug "Levomekol"

Sample	MIC, mg/mL					
	Gramm-positive		Gramm-negative			Fungi
	S. aureus ATCC 25923	*B. subtilis* ATCC 6633	*E. coli* ATCC 25922	*P. vulgaris* ATCC 4636	*P. aeruginosa* ATCC 27853	*C. albicans* ATCC 653/885
Anhydrous gel "Hypericum-Derm"	0.018	0.018	0.035	0.035	0.035	0.035
H. perforatum extract	0.03	0.03	0.06	0.06	0.06	0.06
C. monogyna extract	0.04	0.04	0.08	0.08	0.08	0.08
α-Arbutin	0.21	0.21	0.50	0.50	0.50	0.50
"Clotrimazole"	0.002	0.002	0.002	0.002	0.002	0.001
Lidocaine hydrochloride	0.16	0.16	0.32	0.32	0.32	0.64
"Levomekol"	0.18	0.18	0.32	0.32	0.18	0.32

of the "Hypericum-Derm" gel may be due to the fact that we use a combination of different groups of compounds that are capable of actively affecting all mechanisms of bacteria and fungi.

Conclusions and prospects for further research. The phytochemical composition of the anhydrous gel "Hypericum-Derm" has been determined: phenolic compounds and flavonoids dominate in the gel, while anthracene derivatives have been found in the smallest amount. The anhydrous gel "Hypericum-Derm" has shown a high antimicrobial effect against gram-positive and gram-negative bacteria, and fungi. Thus, the anhydrous gel "Hypericum-Derm" can be used to treat purulent-necrotic wounds.

Conflict of interests: authors have no conflict of interests to declare.

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