ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

DOI: 10.21802/artm.2021.1.17.84.
UDC 615.322 + 615.28 + 582.991.15 + 616.5-002.3

SEARCH FOR BIOLOGICALLY ACTIVE SUBSTANCES WITH ANTIMICROBIAL AND ANTIBIOTIC POTENTIATING PROPERTIES AMOUNG MEMBERS OF THE GENUS ARTEMISIA AGAINTS THE MAIN PATHOGENS OF INFECTIOUS SKIN LESIONS

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Abstract. Active components of the genus *Artemisia* show a wide range of antimicrobial effect against most bacterial pathogens. In addition, artemisin isolated from wormwood is used to treat chloroquine-resistant malaria. Antimicrobial and antibiotic-potentiating effects of eight aqueous ethanolic extracts (40 %, 70 % and 90 %) aerial part of the genus *Artemisia* aqueous against *S. aureus* and *S. epidermidis* strains with various types of resistance to macrolides, lincosamides, tetracyclines and fluoroquinolones isolated from outpatients with different forms of pyoderma have been researched with agar diffusion micromethod. Determination of effective antimicrobial concentrations of antimicrobials and test extracts against staphylococci have been performed with serial dilutions micromethod. The statistical program "Statistica", computer programs UTHSCSA Image Tool 3.0 and Microsoft Office Excel 2016 have been used for statistical processing of microbiological research results. The pronounced antimicrobial effect of the wormwood extract *Artemisia dracunculus* L. (MIC 125.0 - 250.0 μg/ml) against all *S. aureus* and *S. epidermidis* test strains has been established. Other studied extracts showed much weaker antimicrobial effect (MIC 1000.0 - 1500.0 μg/ml). It was found that the species of staphylococci and the phenotype of resistance of test strains do not affect antimicrobial activity of the studied extracts. We have found that there is no clear correlation between antimicrobial properties of the studied extracts and the phenotype of resistance of staphylococci test-strains. Extracts were equally effective against staphylococcal strains with low level of resistance by efflux of antimicrobial drug and skin isolates with chromosomal resistance. The greatest resistance to BAC of the studied extracts was showed by test strains with a high level of resistance to antibiotics of MLS-group and tetracycline, exhibiting sensitivity only to tarragon wormwood.

Active components of 70, 90 % common mugwort extract *Artemisia vulgaris* L. (increase of the inhibition zone up to 117 – 142 %, $p<0.05$) and southern wormwood extract (increase of the inhibition zone up to 50 – 59 % and 74 – 122 %, respectively, $p<0.05$) showed dose-dependent synergistic interaction with erythromycin. Common mugwort extract (70 %) showed synergistic interaction with ¼ MIC of tetracycline (increase of the inhibition zone up to 100 %) against strains with combined resistance to all studied antimicrobials. For the study we used crude total extracts of medicinal plants (40 %, 70 % and 90 % ethanol), so we expect their significantly higher antimicrobial effect against staphylococcal strains while optimizing the extraction process and subsequent purification. It should be noted that 90 % aqueous ethanol extracts showed significantly better antimicrobial properties compared to 40 % and 70 % extracts. Active compounds of tarragon wormwood *Artemisia dracunculus* L. extract show pronounced antimicrobial effect against *S. aureus* and *S. epidermidis* strains, the main causative agents of infectious skin lesions, with different types of resistance to macrolides, lincosamides, tetracyclines and fluoroquinolones. Dose-dependent synergistic interaction with macrolides of common mugwort *Artemisia vulgaris* L. extracts and southern wormwood *Artemisia abrotanum* L. extract with macrolides (erythromycin) and tetracycline has been revealed.

Keywords: wormwoods, antimicrobial activity, synergistic interaction, staphylococci, pyoderma.

Introduction. Wormwoods (*Artemisia*) - perennial herbs or shrubs belonging to the family Asteraceae include 200 - 500 species. Due to a wide range of properties, including antimicrobial representatives of the genus *Artemisia* have interested scientists in their rich chemical composition and biological diversity, that is why they are actively used in official and folk medicine of Europe and Asia [1, 2].

Problem statement and analysis of recent researches. The active components of wormwood (Artemisia vulgaris) have a pronounced antimicrobial effect, fresh essential oil at a concentration of 1:1000 inhibits the growth of pathogens such as *Pseudomas aeruginosa*, *Klebsiella pneumonia*, *Staphylococcus aureus*. Ethanolic extracts from the leaves of the plant have bactericidal properties against *Stapylococcus aureus, Shigella sonnei, Bacillus subtilis*. The antiseptic effect of wormwood aqueous extract external use against pyoderma pathogens, infected skin wounds, etc. is microbiologically substantiated. The dry powder obtained from ground wormwood sprouts has a similar effect [3].

Another member of the genus annual wormwood (*Artemisia annua*), well known as a source of the unique endoperoxide sesquiterpene lactone, artemisinin, is used to treat chloroquine-resistant cerebral malaria [4]. Artimizin and its derivatives have pronounced antihelicobacter activity against clarithromycin-resistant strains [5, 6, 7]. In addition, artimizin isolated from ethanolic, methanolic and acetone extracts of *Artemisia annua*, has showed antimicrobial effect against periodontal microorganisms:

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Aggregatibacter actinomycetemcomitans, Fusobacterium nucleatum subsp. animalis, Fusobacterium nucleatum subsp. polymorphum and *Prevotella intermedia* [8].

The essential oil of annual wormwood is rich in mono- and sesquiterpenes has an antibacterial effect against gram-positive (Enterococcus, Streptococcus, Staphylococcus, Bacillus and Listeria spp.) and gram-negative bacteria (Escherichia, Shigella, Salmonella, Haemophilus, Klebsiella та Pseudomonas spp.) and antifungal effect (Candida, Saccharomyces, Aspergillus spp.) [4].

Ethanolic and chloroform extracts of Gmelin wormwood (*Artemisia gmelinii*) which contain 13 active ingredients have shown a wide range of antibacterial and antifungal effects against Staphylococcus and Bacillus spp. (MIC 1.25-5 mg/ml) and Candida spp. (MIC 2.5-5 mg/ml) [8].

The aim of research: to study the direct antimicrobial activity and the ability of 8 members of the genus *Artemisia* extracts BAC to influence on the resistance mechanisms development to different groups of antimicrobials against main pathogens of infectious skin lesions.

Materials and methods. Eight members of the genus *Artemisia* aerial part ethanolic extracts (extragent 40%, 70 % and 90 % ethanol) were used for the study.

Test strains of *S. aureus* and *S. epidermidis* isolated from outpatients with various forms of pyoderma, obtaining resistance to antibiotics and chemotherapeutic drugs: macrolides, lincosamides (MLS-group antibiotics), tetracyclines and fluoroquinolones were used for the study (table 1). All skin strains of staphylococci were identified by morphological, cultural and biochemical properties (“STAPHYtest 16”, Lachema, Czech Republic). The susceptibility of staphylococci clinical strains to antimicrobials was determined by the disc diffusion method on Mueller-Hinton medium with 4 % sodium chloride, according to the recommendations of the National Committee for Clinical and Laboratory Standards (NCCLS, USA) [9].

Research of the direct antimicrobial action of plant extracts was carried out using the micromethod of diffusion into agar. Every plant extract (20 µl) was instilled into each well, and 20 µm of 40 %, 70 % and 90 % ethanol was added to the control well [10]. To assess the synergism of the antimicrobial action of the extracts with antimicrobial drugs, they were added to the nutrient agar at a final concentration of $^{1}/_{4}$, $^{1}/_{8}$, $^{1}/_{16}$ MIC for each test strain. After 24 hours of incubation at temperature of 37°C, the diameters of microorganisms’ inhibition zones were compared under the influence of plant extracts on a medium without antimicrobial drug and on media with it’s subbacteriostatic concentrations. The diameters of inhibition zones of microorganisms were determined using the computer program ImageTool 3.0 [11].

Determination of effective antimicrobial concentrations of antimicrobial drugs and test extracts against staphylococci was also performed by the micromethod of serial dilutions in MPB (meat-peptone broth) [12]. Growth of cultures in the wells of polystyrene tablets with different concentrations of antimicrobials and plant extracts was evaluated based on the increase in optical density of the medium (OD_{495}), which was recorded using a multi-mode photometer SynergyTMHTX (SILFTA) at a wavelength of 495 nm for 72 hours incubation. Growth curves were constructed for staphylococcal strains to determine MIC (minimum bacteriostatic concentration) and MBC (minimum bactericidal concentration) of the studied drugs. The MPB inoculated only with microbial culture served as a control.

The statistical program "Statistica", computer programs UTHSCSA ImageTool 3.0 and Microsoft Office Excel 2016 were used for statistical processing of microbiological research results.

Research results and their discussion. The analysis of the obtained results showed that antimicrobial effect against 80 % of the strains was shown by tarragon wormwood *Artemisia dracunculus* L. extract (inhibition zone ≥ 11 mm) (table 2.). When studied by serial dilutions micromethod in MPB, this extract was highly effective against all test strains with different resistance phenotypes, even at dilutions $^{1}/_{160}$ - $^{1}/_{320}$ (MIC value 125.0 - 250.0 µg/ml) (Fig. 1).

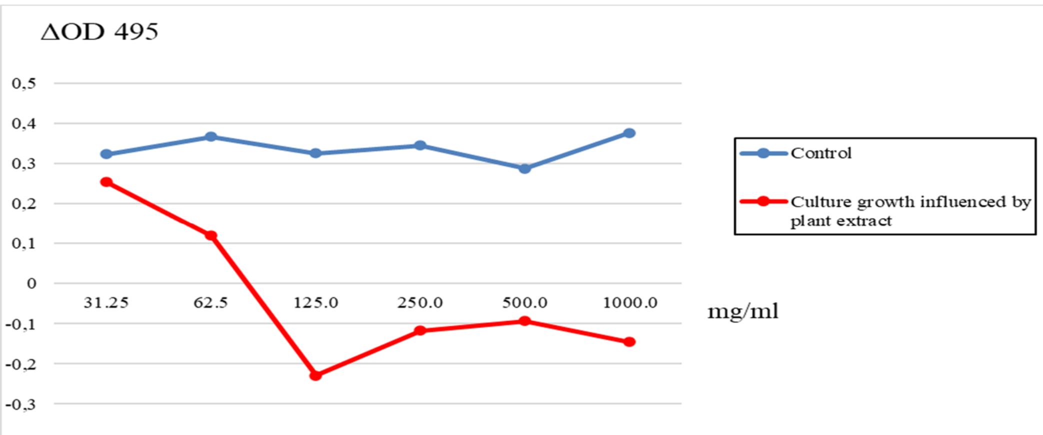

Fig. 1. Growth curves of *S. epidermidis* test strain with combined resistance to all studied antimicrobials in the presence of increasing concentrations of tarragon extract *Artemisia dracunculus* L. Notes: Control - optical density increase of the medium (OD 495) under the influence of staphulococci culture growth without extract (OD 288 – 377).

The main components of the plant are essential oils which contain a number of BAC with antimicrobial properties: methylhavicol (60 - 75 %), sabinene (65 %), cis-o-cimen (10-13 %), nerol, thujone, 1,8-cineole, myrcene, linalool, geraniol, eugenol, phellandrene, tarragon, rutin, flavonoids (3 %), bitter and tannins.

The increase in optical density of the medium due to the growth of test strains of staphylococci under the influence of all studied extracts was much smaller compared to the growth of control cultures. Extracted complexes of common mugwort *Artemisia vulgaris* L. (average value of MIC 1000.0 μg/ml, p <0.05) and southern wormwood (God's tree) *Artemisia abrotanum* L. (average value of MIC 1000.0 μg/ml, p<0.05) showed antimicrobial effect against five test strains, mostly by bacteriostatic effect. Wormwood Lerche extract *Artemisia lerctiana* L., which was effective against 3 skin isolates, showed antimicrobial properties only at a concentration 1200.0 μg/ml by the micromethod of serial dilutions in the PMB. Other test extracts showed antimicrobial effect at concentrations greater than 1500 μg/ml (p <0.05).

Table 1

Effective concentrations (μg/ml) of antimicrobials against test strains of staphylococci with different resistance phenotypes

№	Strain	Resistance phenotype	TET	ERY	CLI	NOR	OFL
1.	*S. aureus*	MLS ind$^-$	2.5	31.25	2.0	1.5	1.0
2.	*S. epidermidis*	MLS ind$^+$, TET	125.0	500.0	200.0	1.0	1.0
3.	*S. epidermidis*	MLS, TET, OFL NOR	31.25	250.0	250.0	6.0	12.5
4.	*S. epidermidis*	MLS ind$^+$	6.25	250.0	125.0	2.5	1.5
5.	*S. epidermidis*	MLS ind$^-$	2.5	125.0	12.5	1.5	1.25
6.	*S. epidermidis*	MLS ind$^+$	1.5	1000.0	64.0	1.25	0.5
7.	*S. aureus*	MLS ind$^-$	1.0	125.0	2.25	2.5	1.0
8.	*S. epidermidis*	OFL NOR	1.5	2.0	1.5	12.5	25.0
9.	*S. epidermidis*	TET	62.5	0.5	1.0	2.5	1.25
10.	*S. aureus*	MLS ind$^+$, TET	62.5	125.0	2.5	1.5	2.5

Notes:
1. MLS ind $^-$ - strains resistant to 14, 15-membered macrolides;
2. MLS ind $^+$ - strains resistant to 14, 15-membered macrolides with induction on lincosamides and 16-membered macrolides;
3. TET - strains resistant to tetracyclines;
4. OFL, NOR - strains resistant to fluoroquinolones.

It should be noted that species of staphylococci does not influence on antimicrobial properties of the studied extracts, as well as *S. aureus* MLS-resistant strains were equally sensitive to BAC of plant extracts, as *S. epidermidis* skin isolates.

In addition, we have found that there is no clear correlation between antimicrobial properties of the studied extracts and the phenotype of resistance of staphylococci test-strains. Extracts were equally effective against staphylococcal strains with low level of resistance by efflux of antimicrobial drug and skin isolates with chromosomal resistance. The greatest resistance to BAC of the studied extracts was showed by test strains with a high level of resistance to antibiotics of MLS-group and tetracycline, exhibiting sensitivity only to tarragon wormwood.

For the study we used crude total extracts of medicinal plants (40 %, 70 % and 90 % ethanol), so we expect their significantly higher antimicrobial effect against staphylococcal strains while optimizing the extraction process and subsequent purification. It should be noted that 90 % aqueous ethanol extracts showed significantly better antimicrobial properties compared to 40 % and 70 % extracts.

Some of the studied extracts showed synergistic interaction with ERY against staphylococci with different types of MLS-resistance. Modifiers of staphylococci MLS-resistance were found among extracted complexes of 70 % common mugwort extract (increase of inhibition zone 117 – 142 %; p <0.05) and 70, 90 % extracts of southern wormwood (God's tree) (increase of inhibition zone 50 – 59 % and 74 – 122 % respectively, p<0.05). These extracts did not show appreciable direct antimicrobial effect under the conditions of our experiments. Common mugwort extract (90%) showed dose-dependent synergistic interaction with ERY (increase of inhibition zone 43 – 86 %; p<0.05) and antimicrobial effect.

Dose-dependent synergistic interaction with ERY subbacteriostatic concentrations against strains with low levels of MLS-resistance indicates presence in plant extracts MLS-resistance modifiers which are inhibitors of the efflux pump of macrolides MsrA, it belongs to the superfamily ATP-dependent membrane ABC-transporters (ATP-binding cassette). However, the antibiotic-potentiating effect of BAC of studied extracts against strains with inductive phenotype indicates their ability to reduce ribosomal meshanisms of resistance, which occurs due to modification of 23S-rRNA by enzyme methyltransferase [13].

Southern wormwood extract (God's tree) (70 %) without showing direct antimicrobial effect against test strains with combined resistance to all studied

ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

antimicrobial drugs showed a synergistic interaction with ¼ MIC of tetracycline (increase of the inhibition zone 100%; $p<0.05$).

The occurrence to tetracycline resistance in staphylococci is also based on the presence of efflux pumps (usually TetK, less - TetL), which belong to the superfamily MFS (major facilitator superfamily) [14]. Therefore, it is important to find inhibitors of efflux pumps which can have plant origin.

However, the active efflux of the antimicrobial drug is considered as the first stage of microorganisms' high levels of resistance formation not only to macrolides, tetracyclines but also to other antimicrobial drugs: fluoroquinolones, acridines, cationic compounds of different structure. Therefore, the establishment of clinical isolates mechanisms of resistance is important to ensure rational antibiotic therapy of patients. Further research will be aimed at finding other representatives of Ukraine flora which extracts have valuable antimicrobial and antibiotic-potentiating properties, detailed study of bacterial resistance mechanisms to antimicrobial drugs, finding possible ways to overcome it.

Conclusions:

1. Active compounds of tarragon wormwood *Artemisia dracunculus* L. extract show pronounced antimicrobial effect against *S. aureus* and *S. epidermidis* strains, the main causative agents of infectious skin lesions, with different types of resistance to macrolides, lincosamides, tetracyclines and fluoroquinolones.

2. Dose-dependent synergistic interaction with macrolides of common mugwort *Artemisia vulgaris* L. extracts and southern wormwood *Artemisia abrotanum* L. extract with macrolides (erythromycin) and tetracycline has been revealed.

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ISSN 2521-1455 (Print)
ISSN 2523-4250 (Online)

Table 2

The arithmetic mean values of staphylococci inhibition zones (mm) by studied extracts (M±m)

Plants name	%	Staphylococci strains									
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Sweet wormwood *Artemisia annua* L.	40	10.57±0.98*	0	0	0	0	0	0	0	0	0
	70	10.17±0.78*	0	0	0	0	0	0	0	0	0
	90	10.47±0.24*	0	0	0	0	8.19±0.21	0	0	0	0
Levant wormseed *Artemisia cina* Berg & C.F. Schmidt ex Poljakov	40	[10.44±0.78]	0	0	0	0	0	0	0	0	0
	70	[11.89±1.05]	0	0	0	0	8.78±0.65	0	0	0	0
	90	[12.12±0.32]	0	0	0	0	9.99±0.46	0	0	0	0
Tarragon *Artemisia dracunculus* L.	40	0	0	12.88±0.98*	12.01±0.79*	14.01±0.33*	0	11.78±0.45*	12.01±0.98*	12.02±0.69*	11.05±0.27*
	70	0	0	14.67±0.76*	12.43±0.73*	14.76±1.16*	0	12.98±0.87*	12.65±1.07*	12.58±0.21*	12.74±0.23*
	90	8.07±0.42	7.43±0.30	14.71±0.24*	12.15±0.62*	14.65±1.23*	0	12.56±0.99*	12.35±0.98*	12.45±0.79*	11.57±0.25*
Sea wormwood *Artemisia maritima* L.	40	[11.02±1.35]	0	0	8.98±0.60	0	[8.16±0.70]	0	0	0	0
	70	[11.62±0.56]	0	0	8.90±0.78	0	[8.12±0.46]	0	0	0	0
	90	[11.81±0.63]	0	0	9.53±0.52	0	[8.43±0.96]	0	0	0	0
Lerche wormwood *Artemisia lercheana* Web. ex Stechm.	40	[10.02±0.34]	0	0	7.29±0.74	7.66±0.31	11.42±0.98*	0	0	0	0
	70	[12.17±0.73]	0	0	8.22±0.91	8.45±0.97	12.32±0.58*	0	0	0	0
	90	[12.57±0.43]	0	0	8.21±0.57	[11.30±0.31] 8.15±0.82	12.32±0.58*	0	0	0	0
Common mugwort *Artemisia vulgaris* L.	40	0	0	0	0	0	10.51±0.57*	0	0	0	0
	70	0	[13.96±0.61]	[14.67±0.31] 8.72±0.31	7.11±0.1	0	11.44±0.56*	8.02±0.74	[14.22±0.33]	0	0
	90	0	0	0	0	14.48±1.00*	11.51±0.50*	8.88±1.15	0	0	0
Absinthe wormwood *Artemisia absinthium* L.	40	0	0	0	0	0	0	0	0	0	0
	70	0	0	0	0	7.38±0.65	0	0	0	0	0
	90	0	[7.07±0.25]	0	0	15.36±0.78*	0	0	0	0	0
Southern wormwood *Artemisia abrotanum* L.	40	0	0	10.67±0.65*	0	0	0	9.19±0.7	0	0	0
	70	0	[8.26±0.56]	9.04±0.27	0	0	[11.34±1.15]	14.98±0.41*	10.69±0.34*	0	0
	90	0	[10.8±0.38]	0	0	14.40±0.83*	[12.01±0.63]	12.81±1.07*	8.07±0.87	0	0

Notes:
1. * - p <0.05** in comparison with inhibition zone of the extractant.
2. The partial inhibition zones of microorganism growth are given in square brackets.
3. Inhibition zone <7.00 mm, which corresponds to inhibition zone around ethanol (control) were not taken into account.

УДК 615.322+615.28+582.991.15+616.5-002.3

ПОШУК БІОЛОГІЧНО АКТИВНИХ РЕЧОВИН З ПРОТИМІКРОБНИМИ ТА АНТИБІОТИКОПО-ТЕНЦІЮЮЧИМИ ВЛАСТИВОСТЯМИ У ПРЕДСТАВНИКІВ РОДУ *ARTEMISIA* ЩОДО ОСНОВНИХ ЗБУДНИКІВ ІНФЕКЦІЙНИХ УРАЖЕНЬ ШКІРИ

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Резюме. Мікрометодом дифузії в агар досліджено протимікробну та антибіотикопотенціюючу активність екстрактів надземної частини 8-ми представників роду *Artemisia* на 40 %, 70 % та 90 % водному етанолі щодо шкірних ізолятів *S. aureus* та *S. epidermidis* з резистентністю до макролідів, лінкозамідів, тетрациклінів та фторхінолонів. Визначення ефективних протимікробних концентрацій протимікробних препаратів та досліджуваних екстрактів проводили мікрометодом серійних розведень. Встановлено виражену протимікробну активність екстракту полину естрагонного *Artemisia dracunculus* L. (МБсК 125,0 – 250,0 мкг/мл) щодо усіх тест штамів *S. aureus* та *S. epidermidis.* Інші досліджувані екстракти проявили значно слабшу протимікробну дію (МБсК 1000,0 – 1500,0 мкг/мл). Виявлено, що видова приналежність стафілококів та фенотип резистентності у тест-штамів не впливають на протимікробну активність досліджуваних екстрактів. Активні компоненти 70, 90 % екстракту полину звичайного *Artemisia vulgaris* L. (збільшення діаметру ЗЗР на 117 – 142 %; p<0,05) та екстракту полину лікарського *Artemisia abrotanum* L. (збільшення діаметру ЗЗР на 50 – 59 % та 74 – 122 % відповідно; p<0,05) проявляють дозозалежний синергізм з еритроміцином. Екстракт полину лікарського (70%) у тест-штамів з поєднаною стійкістю до всіх досліджуваних протимікробних препаратів продемонстрував синергічну взаємодію з ¼ МБсК тетрацикліну (збільшення діаметру ЗЗР на 100 %; p<0,05). Екстраговані комплекси екстракту полину естрагонного проявляють виражену протимікробну активність щодо штамів *S. aureus* та *S. epidermidis* з різним рівнем резистентності до макролідів, лінкозамідів, тетрациклінів та фторхінолонів. Виявлено дозозалежний синергізм протимікробної дії з макролідами в екстракту полину звичайного та екстракту полину лікарського з макролідами та тетрацикліном.

Ключові слова: полини, антимікробна активність, синергічна взаємодія, стафілококи, піодермії.

УДК 615.322+615.28+582.991.15+616.5-002.3

ПОИСК БИОЛОГИЧЕСКИ АКТИВНЫХ ВЕЩЕСТВ ИЗ ПРОТИВОМИКРОБНЫМИ И АНТИБИОТИКОПОТЕНЦИИРУЮЩИМИ СВОЙСТВАМИ В ПРЕДСТАВИТЕЛЕЙ РОДА *ARTEMISIA* ОТНОСИТЕЛЬНО ОСНОВНЫХ ВОЗБУДИТЕЛЕЙ ИНФЕКЦИОННЫХ ПОРАЖЕНИЙ КОЖИ

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Резюме. Микрометодом диффузии в агар исследована противомикробная и антибиотикопотенциирующая активность экстрактов надземной части 8-ми представителей рода *Artemisia* на 40%, 70% и 90% водном этаноле относительно кожных изолятов *S. aureus* и *S. epidermidis* с резистентностью к макролидам, линкозамидам, тетрациклинам и фторхинолонам. Определение эффективных противомикробных концентраций противомикробных препаратов и исследуемых экстрактов проводили микрометодом серийных разведений. Установлено выраженное противомикробное действие экстракта полыни эстрагонного *Artemisia dracunculus* L. (МБсК 125,0 - 250,0 мкг/мл) относительно всех тест штаммов *S. aureus* и *S. epidermidis.* Другие исследуемые экстракты показали значительно более слабое противомикробное действие (МБсК 1000,0 - 1500,0 мкг/мл). Выявлено, что видовая принадлежность стафилококков и фенотип резистентности в тест-штаммах не влияют на противомикробную активностью исследуемых экстрактов. Активные компоненты 70, 90 % экстракта полыни обыкновенной *Artemisia vulgaris* L. (увеличение диаметра ЗЗР на 117 – 142 %; p <0,05) и экстракта полыни лекарственной *Artemisia abrotanum* L. (увеличение диаметра ЗЗР на 50 – 59 % и 74-122 % соответственно; p <0,05) проявляют дозозависимый синергизм с эритромицином. Экстракт полыни лекарственной (70 %) в тест-штаммах с сочетанной устойчивостью ко всем исследуемым противомикробным препаратам продемонстрировал синергическое взаимодействие с ¼ МБсК тетрациклина (увеличение диаметра ЗЗР на 100 %; p <0,05). Извлеченные комплексы экстракта полыни эстрагонного проявляют выраженную противомикробную активность в отношении штаммов *S. aureus* и *S. epidermidis* с различным уровнем резистентности к макролидам, линкозамидам, тетрациклинам и фторхинолонам. Выявлено дозозависимый синергизм противомикробного действия с макролидами в экстракте полыни обыкновенной и в экстракте полыни лекарственной с макролидами и тетрациклинами.

Ключевые слова: полынь, антимикробная активность, синергическое взаимодействие, стафилококки, пиодермии.

Стаття надійшла в редакцію 10.02.2021 р.