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SYNERGISTIC INTERACTION OF MEDICINAL PLANT ETHANOLIC EXTRACTS WITH ERYTHROMYCIN AGAINST SKIN STRAINS OF STAPHYLOCOCCI WITH INDUCIBLE PHENOTYPE OF MLS-RESISTANCE

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Introduction. One of the main ways to control microorganisms' resistance to antibiotics is to find substances that are able to overcome it and potentiate antibiotics action, in particular to neutralize the antibiotic-inactivating enzymes [1, 2] or block the active efflux of antibiotic from microbial cells [3, 4]. Every year there is a growing interest in the therapeutic potential of herbal active compounds as modifiers of antibiotic resistance including MLS-resistance (macrolide-lincosamide-streptoramin B) [5, 6]. It should be emphasized that a number of biologically active substances of plant origin can potentiate antimicrobial activity of erythromycin (ERY) against MLS-resistant staphylococci. 23-methyl-6-O-desmethylauricepyrone from aromatic herb *Achyrocline satureioides (Lam.) DC.* (family Asteraceae) native to South America exhibits strong antimicrobial activity against MSSA and MRSA and potentiates the antimicrobial activity of ERY against MSSA (FICI 0.19) [7]. Acetone and chloroform extracts of *Indigofera suffruticosa Mill*. leaves (which grows in Central and South America, known as anil, and is a source of natural dye for the textile industry) exhibit synergistic effect with ERY against macrolide resistant and sensitive *S. aureus* strains (FICI ≤0.5) [8]. Diosmetin, a natural flavonoid found in various citrus fruits, potentiates the activity of ERY against ABC-pump overexpressed MRSA - RN4220/pUL5054 (FICI 0.28) [9]. Properties of MsrA efflux pump inhibitors have been shown by ethanolic extract of *Portulaca oleracea L.* (FICI with ERY 0.38), its active components were linoleic and oleic acids (FICI 0.12 and 0.18 respectively) [10]. Indole-3-carbinol derived from cruciferous plants extracts (including cabbage and broccoli) increases sensitivity to ERY of biofilm-producing *S. aureus* [11]. The same properties has plant sequiterpenoid germacrene D [12]. Carvacrol from essential oils of *Origanum vulgare L.* and *Thymus vulgaris L.* (Lamiaceae family) shows a strong synergistic interaction with erythromycin against group A streptococci with inducible (ribosomal) phenotypetype of MLS-resistance (FICI <0.5) [13].

Medicinal plants of the Ukrainian flora aiming to restore sensitivity of staphylococci to macrolides were not studied. It is of great practical importance the possibility to overcome MLS-resistance of staphylococci with inducible mechanism that is determined by modification of ribosomal 23S-rRNA at the expense of methyltransferase action (enzyme that is the product of an *erm* genes family that encode a high level of resistance to macrolides) [14]. As to our data, about 4% of *S. aureus* and about 56% of *S. epidermidis* skin isolates have this phenotype. In addition, another 16% of *S. aureus* isolates and 5% of *S. epidermidis* have full resistance to antibiotics of MLS family. [15].

The aim of this investigation was to establish the antimicrobial and synergistic concentrations of combinations of ERY with eight ethanolic extracts (90% ethanol), which have been selected on a basis of primary microbiological screening, against skin isolates of *S. epidermidis* and *S. aureus* with inducible phenotype of MLS-resistance.

Materials and methods

Plant collection and identification.

Samples of eight plants (table 1) were collected in Western Ukraine and authenticated by morphological properties [16] at Department of Microbiology, Virology and Immunology Ivano-Frankivsk National Medical University.

Plant extraction and preparation.

The plant materials were air dried and ground to coarse powder for extraction. Each sample was extracted with 90% ethanol for two weeks at room temperature (plant material/ethanol 1:10). To obtain plant extracts insoluble residue was filtered and solvent was added to get initial volume.

Microorganisms. Susceptibility testing.

Seven skin isolates of *S. aureus* and *S. epidermidis* with inducible phenotype of MLS-resistance were used for research. Identification of tested strains was carried out according to "Bergey's Manual" [17] by morphological, cultural and biochemical properties («STAPHYtest 16», Lachema, Czech Republic).

S. aureus and *S. epidermidis* strains were tested for susceptibility to antibiotics by disk diffusion test on Mueller-Hinton plate agar according to NCCLS guidelines [18]. MLS-phenotype of staphylococci was identified by six antibiotics: erythromycin (ERY, 15 μg/disk, clarithromycin (CTM, 15 μg/disk) roxitromycin (ROX, 30 μg/disk), spiramycin (SR, 30 μg/disk), lincomycin (LM 15 μg/disk) and clindamycin (CLI, 2 μg/disk). To differentiate constitutive and inducible MLS-resistance of staphylococci 14-membered macrolides (erythromycin and clarithromycin), 16-membered macrolide spiramycin, lincosamides (clindamycin and lincomycin) were used. [19]. Disks with antibiotics for disk diffusion induction testing were placed 12 mm apart (edge to edge) (according NCCLS guidelines). Zone diameters were recorded at 16-18 and 24 h for all disks using transmitted and reflected light. MICs and MBCs of ERY were studied by two-fold dilution of ERY on Mueller-Hinton plate agar. Cultures growth was detected at 24 to 36 h.

Effective antimicrobial concentrations of plant extracts were determined by two-fold serial dilution in nutrient agar starting with the ratio 1:10 to exclude the antimicrobial activity of 90% ethanol. Microbial cultures growth was assessed after incubation for 24 hours at 37°C (MIC) and after additional three days at room temperature (MBC). The final values of plant extracts effective concentrations against each strain were calculated taking

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into account the weight of dry residue after evaporation of 1.0 ml of extract at room temperature.

Checkerboard assay and fractional inhibitory concentration. Synergistic effects of plant extracts and ERY dual combinations were assessed using the checkerboard assay against tested strains [20].

Two rows of petri plates with nutrient agar (10 mL) were prepared for each extract. 0.5 mL of antibiotic in a final concentration $^1/_4$ MIC for each tested strain and 0.5 mL of studied extract in different two-fold dilutions ranging from $^1/_4$ MIC were added to the first row of petri plates with nutrient agar. 0.5 mL of the studied extract in a final concentration $^1/_4$ MIC for each tested strain and 0.5 mL of the antibiotic in different two-fold dilutions ranging from $^1/_4$ MIC were added to the second row of petri plates with nutrient agar. 1.0 mL of a mixture DMSO:ethanol was added to the control plates. Bacterial suspensions were prepared from each *S. aureus* and *S. epidermidis* strains freshly grown in Mueller-Hinton agar (approximately 1×10^7 CFU/ mL). Nutrient agar with dual combinations of tested substances was inoculated with bacterial cultures using replicator. After incubation at 37°C for 24 h, bacterial growth was recorded by visual growth.

Synergistic interaction of *Alnus incana L.* fruits extract with ERY against *S. aureus* strains with inducible phenotype of MLS-resistance was also tested by a broth microdilution susceptibility assay [21]. Bacterial growth as increase of the medium optical density (wavelength 495 nm) was recorded using microplate reader AKI-01-C. The data were used to build growth curves and for determination of fractional inhibitory concentration (MIC and MBC of investigated substances combinations). Control wells contained broth and microbial culture.

The Fractional inhibitory concentration index (FICI) was calculated according to the equation:

$$FICI = \frac{MIC(E+ERY)}{MIC(E)} + \frac{MIC(ERY+E)}{MIC(ERY)},$$

MIC(E+ERY): minimal inhibitory concentration of extract in combination with erythromycin; MIC(ERY+E): minimal inhibitory concentration of erythromycin in combination with extract. Results were considered: synergistic (FIC < 0.5); additive (0.5 < FIC < 1); non-interactive (1 < FIC < 4); or antagonist (FIC > 4). Each experiment was performed in triplicate.

Statistical analysis. Results are expressed as the mean ± standard deviation (SD). Statistical analyses were performed by ANOVA and Microsoft Office Excel 2003.

Results and discussion. Earlier we have reported about dose-dependent synergistic effect of aqueous-ethanolic extracts of *Alnus incana L.* fruits, *Betula verrucosa L.* buds, *Geranium pratense L.* rhizomes, *Arctostaphylos uva-ursi (L.) Spreng.* leaves, *Tamarix ramosissima Ledeb.* leaves, *Sanguisorba officinalis L.* roots, *Biota orientalis (L.) Endl. (Platycladus orientalis (L.) Franco)* fruits with ERY (at $^1/_{64}$ and $^1/_4$ MIC) against *S. aureus* and *S. epidermidis* strains with constitutive and inducible phenotypes of MLS-resistance by agar diffusion method [22].

MIC of studied extracts against tested strains were in the range of 40.625-2,600 μg/mL, MIC_{50} - 162.5-2,600 μg/mL. The *Alnus incana L.* fruits extract was the most potent inhibitor of tested strains (MIC 40.625-162.5 μg/mL). Its bactericidal action was detected in dilutions 1:40 - 1:160, bacteriostatic - in dilutions 1:80 - 1:320. *Geranium pratense L.* rhizomes extract exhibited the least antimicrobial activity (MIC 650-2,600 μg/mL) (Table 1).

In the presence of $^1/_4$ MIC of ERY antimicrobial concentration of *Alnus incana L.* fruits extract was decreased in 32-64 times and *Geranium pratense L.* rhizomes extract antimicrobial concentration was decreased in 64-256 times (Table 2).

When the antimicrobial actions of erythromycin and eight ethanolic extracts were tested in dual combinations, additive, synergic and non-interactive actions were observed (Table 3); importantly, no antagonistic effects were noted.

Alnus incana L. fruits extract and the *Geranium pratense L.* rhizomes extract showed synergy with erythromycin against 100% strains of staphylococci (average FICI 0.028 - 0.057; $p<0.001$). After incubation for 24 and 36 hours in the presence of $^1/_4$ - $^1/_{16}$ MIC *Alnus incana L.* fruits extract with ERY in concentrations range of 1,000 – 2,000 μg/mL (MIC of ERY for this strain – 4,000 μg/mL, MBC – 8,000 μg/mL) almost complete inhibition of *S. epidermidis* with inducible phenotype MLS-resistance was observed (fig. 1).

Table 1. MIC of ERY and aqueous-ethanolic extracts (µg/mL) of plants against *S. aureus* and *S. epidermidis* skin strains.

№	Strains	MLS phenotype	MIC ERY	Plant extracts							
				1	2	3	4	5	6	7	8
1.	*S.aureus*	D	1,000	162.5	400	112.5	575	281.25	650	600	1,700
2.	*S.aureus*	R	500	40.625	100	56.25	143.75	281.25	2,600	300	850
3.	*S.aureus*	R	2,000	162.5	400	225	575	562.5	2,600	1,200	1,700
4.	*S.aureus*	R	500	162.5	100	225	575	1,125	1,300	600	1,700
5.	*S.epidermidis*	R	1,000	162.5	200	225	575	562.5	650	600	1,700
6.	*S.epidermidis*	D	1,000	81.25	200	112.5	287.5	281.25	2,600	600	1,700
7.	*S.epidermidis*	D	1,000	162.5	200	225	575	281.25	2,600	600	1,700
8.	MIC_{50}		1,000	162.5	200	225	575	281.25	2,600	600	1,700
9.	MIC_{90}		1,000	162.5	200	225	575	562.5	2,600	600	1,700

1. MIC_{50} – minimum inhibitory concentration for 50% of strains;
2. MIC_{90} - minimum inhibitory concentration for 90% of strains;
3. Plant extracts: 1 - *Alnus incana L.* fruits, 2 - *Biota orientalis (L.) Endl*. (*Platycladus orientalis (L.) Franco*) fruits, 3 - *Cotinus coggygria Scop.* (*Rhus cotinus R.*) leaves, 4 - *Arctostaphylos uva-ursi (L.) Spreng*. leaves, 5 - *Betula verrucosa L*. buds, 6 - *Geranium pratense L*. rhizomes, 7 - *Sanguisorba officinalis L*. roots, 8 - *Tamarix ramosissima Ledeb*. leaves.

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Table 2. Fold reduction of plant extracts MIC in dual combinations with ERY in subinhibitory concentrations against skin isolates of staphylococci with inducible phenotype of MLS-resistance.

№	Strains	1/4 MIC ERY	Organic extracts																	
			1			2			3			4			5			6		
			MIC_E	MIC_E + 1/4 MIC_{ERY}	Fold reduction of extract MIC	MIC_E	MIC_E + 1/4 MIC_{ERY}	Fold reduction of extract MIC	MIC_E	MIC_E + 1/4 MIC_{ERY}	Fold reduction of extract MIC	MIC_E	MIC_E + 1/4 MIC_{ERY}	Fold reduction of extract MIC	MIC_E	MIC_E + 1/4 MIC_{ERY}	Fold reduction of extract MIC	MIC_E	MIC_E + 1/4 MIC_{ERY}	Fold reduction of extract MIC
1.	*S.aureus*	250	1:80	1:5,120	64	1:40	1:2,560	64	1:160	1:640	4	1:40	1:5,120	128	1:10	1:1,280	128	1:40	1:320	8
2.	*S.aureus*	125	1:320	<1:5,120	>16	1:10	1:2,560	256	1:160	1:640	4	1:160	<1:5,120	>32	1:20	1:1,280	64	1:80	1:160	2
3.	*S.aureus*	500	1:80	1:5,120	64	1:10	1:2,560	256	1:80	1:640	8	1:40	1:320	8	1:10	1:1,280	128	1:20	1:160	8
4.	*S.aureus*	125	1:80	1:5,120	64	1:20	1:2,560	128	1:40	1:640	16	1:40	1:5,120	128	1:10	1:1,280	128	1:40	1:160	4
5.	*S.epidermidis*	250	1:80	1:5,120	64	1:40	1:2,560	64	1:80	1:80	1	1:40	1:320	8	1:10	1:80	8	1:40	1:160	4
6.	*S.epidermidis*	250	1:160	1:5,120	32	1:10	1:2,560	256	1:160	1:640	4	1:80	1:5,120	64	1:10	1:80	8	1:40	1:160	4
7.	*S.epidermidis*	250	1:80	1:5,120	64	1:10	1:640	64	1:80	1:80	1	1:40	1:5,120	128	1:10	1:1,280	128	1:40	1:320	8

Plant extracts: 1 - *Alnus incana L.* fruits, 2 - *Geranium pratense L.*, 3 - *Betula verrucosa L.* buds, 4 - *Arctostaphylos uva-ursi (L.) Spreng.* leaves, 5 - *Tamarix ramosissima Ledeb.* leaves, 6 - *Sanguisorba officinalis L.* roots.

Table 3. FICI of dual combinations of plant extracts with ERY in subinhibitory concentrations against skin isolates *S. aureus* and *S. epidermidis* with inducible phenotype of MLS-resistance

№	Strains	Plant extracts							
		1	2	3	4	5	6	7	8
1.	*S.aureus*	0.048	2.0	2.0	0.012	0.325	0.024	0.500	0.012
2.	*S.aureus*	0.080	2.0	2.0	0.038	0.450	0.020	1.500	0.023
3.	*S.aureus*	0.032	2.0	2.0	0.250	0.262	0.012	0.250	0.010
4.	*S.aureus*	0.080	2.0	2.0	0.508	0.450	0.040	0.750	0.016
5.	*S.epidermidis*	0.048	2.0	2.0	0.157	0.750	0.032	1.250	0.625
6.	*S.epidermidis*	0.064	2.0	2.0	0.024	0.325	0.020	1.250	0.012
7.	*S.epidermidis*	0.048	2.0	2.0	0.012	0.750	0.048	0.189	0.625
8.	Average FICI	0.057±0.02	2.0±0.0	2.0±0.0	0.143±0.18	0.473±0.20	0.028±0.01	0.812±0.52	0.189±0.29

Plant extracts: 1 - *Alnus incana L.* fruits, 2 - *Biota orientalis (L.) Endl*. (*Platycladus orientalis (L.) Franco*) fruits, 3 - *Cotinus coggygria Scop*. (*Rhus cotinus R.*) leaves, 4 - *Arctostaphylos uva-ursi (L.) Spreng*. leaves, 5 - *Betula verrucosa L.* buds, 6 - *Geranium pratense L.* rhizomes, 7 - *Sanguisorba officinalis L.* roots, 8 - *Tamarix ramosissima Ledeb*. leaves.

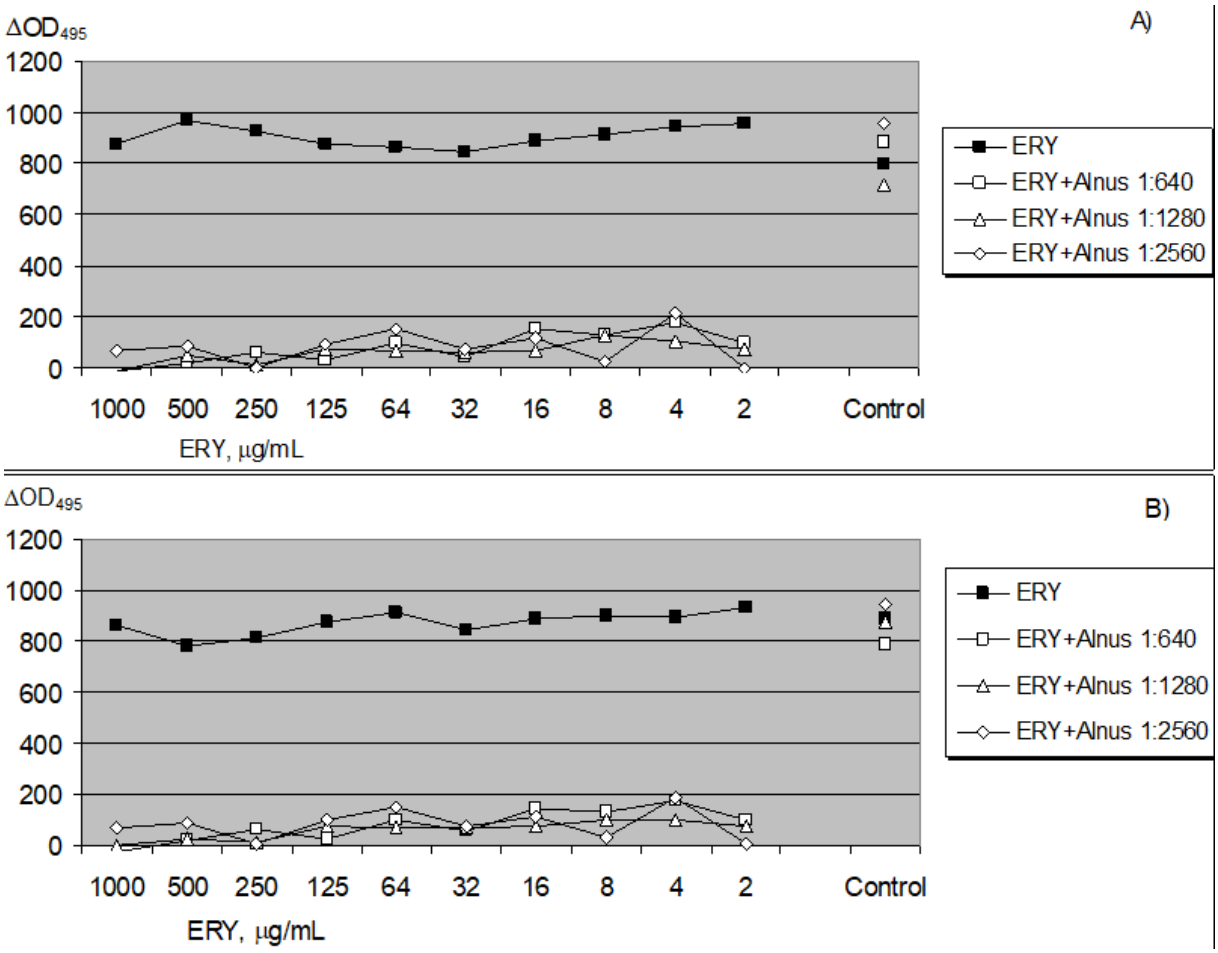

Figure 1. Growth of *S. epidermidis* with inducible phenotype (D) of MLS-resistance in the presence of dual combinations of *Alnus incana L.* fruits extract with ERY in subinhibitory concentrations: A) 24 hours of incubation; B) 36 hours of incubation.

Aqueous-ethanolic extracts of *Betula verrucosa L.* buds (average FICI 0.473±0.20), *Arctostaphylos uva-ursi (L.)* Spreng. leaves (average FICI 0.143±0.18) and *Tamarix ramosissima Ledeb.* leaves (average FICI 0.189±0.29) showed synergic action with erythromycin against 71.4-85.7% tested strains. Extract of *Sanguisorba officinalis L.* root showed non-interactive action with antibiotic against 42.8% isolates of staphylococci. Additive interaction with erythromycin for this extract was observed against 28.6% and synergic action against 28.6% strains (average FICI 0.812±0.52).

Checkerboard titration method used in this research provides a more accurate and reliable data on the synergistic interaction of medicines antimicrobial activity. Our previous researches by qualitative screening test showed a possible synergy of *Biota orientalis (L.) Endl. (Platycladus orientalis (L.) Franco)* fruits and *Cotinus coggygria Scop. (Rhus cotinus R.)* leaves extracts with erythromycin. However, this assumption was not confirmed while testing those extracts by checkerboard titration method. Both extracts in combination with erythromycin exhibited non-interactive action against 100% tested strains (average FICI 2.0±0.0) (Table. 3). The results of our research indicate that neither species nor MLS-resistance phenotype of skin staphylococci does not influence on antimicrobial activity of plant extracts and their ability to restore sensitivity to ERY of microbial culture.

Macrolide antibiotics are widely used for the treatment of pyoderma, infections of upper respiratory tract and bronchopulmonary system, and are included to the treatment regimen of ulcer [21, 23]. Thus, sensitivity decrease of staphylococci, streptococci, pneumococci and helicobacter to erythromycin and its semi-synthetic analogues is obvious. From the microbiological point of view, semisynthetic macrolides possessing better pharmacokinetic and pharmacodynamic characteristics don't have special advantages over erythromycin, as microorganisms acquire cross-resistance which is provided by the same mechanisms. Therefore, one of the possible solutions of the problem is the combined use of antimicrobial agents that contain antibiotic and resistance modifier (antimicrobial adjuvant) [6]. Research of antibiotics combinations with bioactive compounds of natural origin is promising to overcome the increasing bacterial resistance and MLS-resistance.

Over the last decade in world literature number of publications devoted to the study of synergistic interaction

of plant extracts and their components with antibiotics due to the influence on efflux mechanisms of microbial resistance appeared. Many substances of plant origin are identified as inhibitors of staphylococcal NorA efflux pump, which increase susceptibility to fluoroquinolones. However, synergy of plant compounds with macrolides is studied much less. Taxifolin-7-O-α-L-ramnopyranozide isolated from *Hypericum japonicum Thunb*., potentiates antimicrobial activity of azithromycin against MRSA [5]. Diosmetin (found in citrus fruits), linoleic and oleic acids (purified from *Portulaca oleracea L.*) are active inhibitors of MsrA pump in MRSA with associated MLS-resistance [9, 10]. Geraniol, the active compound of *Helichrysum italicum (Roth.) G. Don* essential oil, significantly increases the sensitivity of *S. aureus, E. aerogenes, A. baumannii* та *P. aeruginosa* multiresistant strains to fluoroquinolones and chloramphenicol by blocking efflux mechanisms of resistance, as well as to β-lactam antibiotics [4]. Carvacrol (derived from the essential oils of *Origanum vulgare L.* and *Thymus vulgaris L.*) potentiates *in vitro* antimicrobial activity of ERY (FICI <0,5) against group A streptococci with combined MLS-resistance determined by erm(TR)/iMLS, erm(B)/iMLS, erm(B)/cMLS and mef(A)/M genes [13].

Macrolides are commonly used in therapeutic regimens of peptic ulcer treatment for eradication of *Helicobacter pylori*, which has led to significant spread of resistant strains [27, 28]. Therefore, it is of great interest investigation on the synergistic interaction of plant extracts with macrolides against *H. pylori* resistant strains. In particular combination of clarithromycin with *Zingiber officinale Rosc.* extract (average FICI 0.52) and propolis extract (average FICI 0.51) have exhibited improved inhibition of *Helicobacter pylori* with synergistic or additive activity [24]. Pyrenyl ester derived from *Eucalyptus torelliana F. Muell*. leaves extract enhanced the activity of clarithromycin, its MIC value was reduced twofold against resistant strains of *H. pylori* (additive effect was observed, average FICI 0.75) [25]. Epigallocatechin gallate Isolated from numerous medicinal plants extracts provides 4-64-fold reduction of azithromycin and clarithromycin MIC against *Campylobacter coli* and *C. jejuni* strains with efflux mechanisms of resistance [26].

For the first time we performed screening test by agar diffusion method to evaluate antimicrobial and synergic activity of 242 extracts of various organs (aerial parts, leaves, buds, fruit, roots and rhizomes) of 183 medicinal and aromatic plants against staphylococci with different mechanisms of MLS-resistance [22]. Qualitative screening test allowed to select the plants that potentially contain compounds with properties of modifiers of staphylococcal macrolides resistance. The selected plant extracts were tested by checkerboard assay. It allows to obtain more accurate information about interaction of antimicrobials. Presented results confirmed that ethanol extract of *Alnus incana L.* fruits, *Geranium pratense L.* rhizomes, *Betula verrucosa L.* buds, *Arctostaphylos uva-ursi (L.) Spreng*. leaves and *Tamarix ramosissima Ledeb*. leaves significantly reduced sensitivity to erythromycin of both *S. epidermidis* and *S. aureus* strains with ribosomal mechanism of MLS-resistance.

Obviously, the main target of synergistic combination of ERY with plant extracts bioactive compounds against microorganisms with inducible phenotype of MLS-resistance is enzyme adenine-N^6-methyltransferase – product of *erm* genes family, providing modification of ribosomal 23S-rRNA in macrolide binding site [26-28]. We can make assumptions that bioactive compounds of plant extracts can either block the active center of this enzyme or suppress expression of *erm* genes.

Experimental data indicate that combination of plant extracts with macrolides in therapeutic regimens against MLS-resistant staphylococci is promising, particularly for the treatment of pyoderma. The introduction of combined chemotherapy in clinical practice can actually help to solve two problems of modern medicine – slowing of antibiotics resistance acquisition by microorganisms and improving treatment of infections caused by resistant strains. We hope that detection of antibiotic resistance modifiers in certain plant extracts will increase the interest to intensive phytochemical studies for isolation and identification of their active components. It will be a basis for the future investigations of mechanisms of this synergy on molecular level.

Conclusion

1. BAC of medicinal and aromatic plants potentiate antimicrobial activity of macrolides against skin isolates of staphylococci with inducible MLS-resistance.
2. *Alnus incana L.* fruits ethanolic extract demonstrates the best direct antimicrobial activity and in combination with ERY synergistically inhibits the growth of *S. aureus* and *S. epidermidis* MLS-resistant strains.
3. Ethanolic extracts of *Geranium pratense L.* rhizomes, *Arctostaphylos uva-ursi (L.)* Spreng. leaves, *Tamarix ramosissima Ledeb*. leaves and *Betula verrucosa L.* buds also exhibit synergistic effect with ERY against skin isolates of staphylococci with inducible MLS-resistance.

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SYNERGISTIC EFFECTS OF ETHANOL MEDICINAL PLANT EXTRACTS WITH ERYTHROMYCIN AGAINST SKIN STRAINS OF STAPHYLOCOCCI WITH INDUCIBLE PHENOTYPE OF MLS-RESISTANCE

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Introduction. One of the main ways to control microorganisms' resistance to antibiotics is to find substances that are able to overcome it and potentiate antibiotics action, in particular to neutralize the antibiotic-inactivating enzymes or block the active efflux of antibiotic from microbial cells. Every year there is a growing interest in the therapeutic potential of herbal active compounds as modifiers of antibiotic resistance including MLS-resistance (macrolide-lincosamide-streptoramin B). It should be emphasized that a number of biologically active substances of plant origin can potentiate antimicrobial activity of erythromycin (ERY) against MLS-resistant staphylococci. The present study was designed to investigate the antibacterial and synergistic effects of eight Ukrainian ethanol medicinal plant extracts with erythromycin against skin strains of staphylococci with inducible phenotype of MLS-resistance. **Material & methods.** *S. aureus* and *S. epidermidis* strains were tested for susceptibility to antibiotics of MLS-group by disk diffusion test. Effective antimicrobial concentrations of plant extracts and erythromycin were determined by two-fold serial dilution in nutrient agar and broth. Combinatory effects between organic extracts and ERY were assessed using the checkerboard assay against tested strains to evaluate culture growth in the presence of two antimicrobials with different concentrations. **Results & discussion.** The *Alnus incana L*. fruits extract was the most potent inhibitor against tested strains (MIC 40.625-162.5 μg/mL); while *Geranium pratense L*. rhizomes extract exhibited the least antimicrobial activity (MIC 650-2,600 μg/mL). The *Alnus incana L.* fruits extract and the *Geranium pratense L*. rhizomes extract showed synergistic effect with erythromycin against 100% strains of staphylococci (average FICI 0.028 – 0.057; $p<0.001$). In the presence of $^1/_4$ MIC of ERY *Alnus incana L.* fruits extract antimicrobial concentration was decreased in 32-64 times and Geranium pratense L. rhizomes extract antimicrobial concentration was decreased in 64-256 times. Ethanol extracts of *Betula verrucosa L*. buds (average FICI 0.473±0.20), *Arctostaphylos uva-ursi (L.) Spreng*. leaves (average FICI 0.143±0.18) and *Tamarix ramosissima Ledeb*. leaves (average FICI 0.189±0.29) showed synergic action with erythromycin against 71.4-85.7% tested strains. Ethanol extracts of *Sanguisorba officinalis L*. roots showed non-interactive action with antibiotic against 42.8% isolates of staphylococci. Additive interaction with erythromycin for this extract was observed against 28.6% and synergic action against 28.6% strains (average FICI 0.812±0.52). *Biota orientalis (L.) Endl*. (*Platycladus orientalis (L.) Franco*) fruits extract and *Cotinus coggygria Scop*. (*Rhus cotinus R*.) leaves extract exhibited non-interactive action with antibiotic against all tested strains (average FICI 2.0±0.0). Experimental data indicate that combination of plant extracts with macrolides in therapeutic regimens against MLS-resistant staphylococci is promising, particularly for the treatment of pyoderma. The introduction of combined chemotherapy in clinical practice can actually help to solve two problems of modern medicine - slow the process of microorganisms (such as staphylococcus) resistance to antibiotics acquiring and improve treatment of infections caused by resistant strains. Detection of bacteria antibiotic resistance modifiers in various plants stimulates to their intensive phytochemical study for isolation and identification of the active components. It will help to investigate the mechanisms of synergy on the molecular level. **Conclusion.** BAC of medicinal and aromatic plants potentiate antimicrobial activity of macrolides against skin isolates of staphylococci with inducible MLS-resistance. *Alnus incana L.* fruits ethanolic extract demonstrates the best direct antimicrobial activity and in combination with ERY synergistically inhibits the growth of *S. aureus* and *S. epidermidis* MLS-resistant strains. Ethanolic extracts of *Geranium pratense L.* rhizomes, *Arctostaphylos uva-ursi (L.)* Spreng. leaves, *Tamarix ramosissima Ledeb*. leaves and *Betula verrucosa L.* buds also exhibit synergistic effect with ERY against skin isolates of staphylococci with inducible MLS-resistance.

Keywords*:* plant extracts, erythromycin, staphylococci, MLS-resistance, synergistic effects.