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SYNERGISM OF ANTIMICROBIAL ACTIVITY OF ANTIBIOTICS WITH BIOCIDES OF NATURAL ORIGIN

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Currently, antibiotic therapy remains the primary method for treating infectious diseases in humans. Nevertheless, its effectiveness is rapidly decreasing due to the widespread emergence of resistant pathogens, necessitating the exploration of new treatment options. One potential approach involves the use of antibiotics in combination with other natural compounds.

The aim of the review was to summarize the literature data on the synergy of the antimicrobial action of combinations of antibiotics with various biocides against Gram-positive and Gram-negative pathogenic microorganisms.

The analysis of literature data has shown that promising compounds for use in combinations with antibiotics include essential oils, other plant components, antimicrobial peptides (both natural and synthetic), and microbial surfactants. In the majority of studies, the researchers calculated the fractional inhibitory concentration index, confirming the synergistic antimicrobial activity of antibiotics and the mentioned compounds. The use of natural biocides in combination with commercial antibiotics, particularly against Gram-negative (including methicillin-resistant) *Staphylococcus* species and Gram-positive microorganisms (*Escherichia coli, Pseudomonas aureginosa, Klebsiella pneumoniae, Proteus mirabilis, Acinetobacter baumannii*), enabled to consider these mixtures not only as effective antimicrobial agents but as one of the ways to reduce the effective concentration of antibiotics as well.

It should be noted that in the presented studies, the researchers only observed the synergy of antimicrobial activity between a combination of antibiotics and other biocides, without emphasizing the potential mechanisms of interaction between the components of the complex. This likely depended on various factors, including the qualitative composition of natural compounds. Therefore, it was important to continue research not only on the synergy of antimicrobial activity in compound mixtures but also on the underlying mechanisms of their interaction. This would provide insights to enhance their effectiveness in combating resistant microorganisms.

Key words: antimicrobial effect, pathogenic microorganisms, fractional inhibitory concentration.

Since the early 1990s, the development and commercialization of new antibiotics have significantly slowed down [1, 2]. In the period from 2017 to 2019, the U.S. Food and Drug Administration (FDA) approved 11 antimicrobial drugs, of which only 4 were accepted by the European Medicines Agency (EMA): the combination of meropenem-vaborbactam (Vaborem), eravacycline (Xera), delafloxacin (Baxdela/Quofenix), and the combination of imipenem-cilastatin-relebactam (Recarbrio).

The limited number of new antimicrobial compounds was associated with the emergence of multidrug-resistant bacteria, which, due to their resistance to more than three classes of antibiotics, posed a serious threat to human health [3]. However, systematic international surveillance of the spread of multidrug-resistant pathogens was not conducted. Available reports indicate that over 33,000 deaths annually in Europe are linked to hospital-acquired and community-acquired infections caused by resistant strains [4].

In 2017, the World Health Organization (WHO) published a list of pathogens (ESKAPE) for which new antimicrobial agents were urgently needed. Within this extensive list, *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* species were given "priority status" [4]. This is because they have developed resistance mechanisms to oxazolidinones, lipopeptides, macrolides, fluoroquinolones, tetracyclines, β-lactams, combinations of β-lactam inhibitors and β-lactamases, as well as last-line antibiotics, including carbapenems, glycopeptides, and polymyxins [2, 5–7].

Against the backdrop of the inefficiency of the "classic" approach to combating infectious agents, there is a growing development of a new direction-combined (synergistic) action. This involves the use of antibiotics in combination with other antimicrobial substances, particularly those of natural origin.

This review presents the latest literature data on the synergistic antimicrobial activity of antibiotics and essential oils, antibiotics and natural compounds other than essential oils, antibiotics and antimicrobial peptides, as well as surface-active substances against Gram-positive (methicillin-resistant) strains and Gram-negative pathogens of infectious diseases.

Synergistic effect of a complex of antibiotics with natural biocides on gram-positive bacteria of *Staphylococcus* genus

Antimicrobial activity of a mixture of antibiotics and essential oils. Staphylococcus aureus is a leading cause of both nosocomial and community-acquired infections in humans worldwide. This opportunistic pathogen can cause numerous acute and chronic skin infections, fatal pneumonia, sepsis, meningitis, endocarditis, or toxic shock syndrome [8]. Moreover, the increase in the prevalence of such infections, associated complications and increased mortality are associated specifically with methicillin-resistant (MRSA) strains of *Staphylococcus aureus* [9]. The latter are capable of synthesizing alternative penicillin-binding proteins (PBPs) with low affinity for penicillin, which makes them widely resistant to "traditional" treatments.

Therefore, along with an increase in the number of publications on the spread of such resistant strains and the study of the mechanisms of their resistance [8–10], more and more studies are appearing on alternative strategies and molecules (including those of natural origin) to combat resistant strains of *S. aureus*.

The data on synergism of antimicrobial activity of essential oils (EO) and antibiotics (AB) against to methicillin-resistant strains of *S. aureus* are shown in Table 1. Thus, it was found [11] that the use of essential oils of mastic tree and pituratos green in combination with tetracycline and amoxicillin for *S. aureus* SARM753, it was possible to reduce the minimum inhibitory concentration (MIC) of antibiotics from 16–32 μg/ml to 1–12 μg/ml. A significant decrease in the MIC (32–64 times) of the actibiotics ofloxacin and oxalicin was also observed in the case of using EO obtained from *Teucrium ramosissimum* in relation to the SARM760 strain. The researchers associated this effect with the component composition of essential oils rich in limolene, terpene-4-ol, and b-eudismol. The latter was the main component included only in the composition of *Teucrium ramosissimum* branch, which possibly explainsed the significantly lower MIC values of actibiotics in a mixture with this essential oil.

In a previously published review [12], we emphasized that one of the main methods for establishing synergism was the calculation of fractional inhibitory concentration (FIC), with an FIC value of ≤ 0.5 indicating synergism between compounds. Thus, in work [13] they investigated the possibility of using tea tree essential oil and rifaximin (research was carried out at different pH (7.4, 6.5 and 5.0) to simulate extracellular and intracellular conditions) against 4 strains of *S. aureus*. However, the synergism of antimicrobial activity (FIC value was 0.37, at pH 6.5) was established only for one strain (Table 1), while for three other FICs it exceeded 0.5, which indicated the additive effect of such mixture according to the test cultures studied [13].

The use of a combination of antibiotics

and EO allows not only a reduction in the minimum inhibitory concentration (MIC) of the antibiotic but also of the essential oil itself. In the work [14], synergy of the antimicrobial activity (FIC ≤ 0.06) was observed for the combination of imipenem and basil EO against *Staphylococcus aureus* strains, while the MIC of the latter was reduced by 32 times compared to both test cultures (Table 1). It should be noted that, in addition to imidopyran, synergism was also determined for a mixture of EO and ciprofloxacin, while antagonism of the interaction of such compounds was established for both test cultures [14].

Combinations of cumin EO with ciprofloxacin and amoxicycline [15], peppermint with ampicillin and gentamicin [16], cinnamon with amicillin and levometsit [8] and norfloxacin [19], savory with gentamicin [20] croton with oxacillin and ampicillin [21], are promising for combating methicillin-resistant strains of *Staphylococcus aureus* as evidenced by the FIC indicator (Table 1). It should be noted that in most of the aforementioned studies, researchers attribute the positive effect of combining antibiotics and essential oils to the ability of their main components (terpenes, phenols, alcohols, etc.) to damage the cell membrane, leading to intracellular content extravasation [20–21]. They emphasize that the combined use of essential oils with modern antimicrobial drugs is more effective compared to monotherapy, reducing side effects and the required drug dosage.

Table 1

Antimicrobial effect of a mixture of essential oils with antibiotics against strains *Staphylococcus aureus*

Essential oil, EO (source of obtaining)	Antibiotics (AB)	Strain *Staphylococcus aureus*	MIC EO, μg/ml	MIC AB, μg/ml	MIC of the components in the mixture, μg/ml			Reference
					EO	AB	FIC	
Pistacia lentiscus (Mastic tree)	Tetracycline	SARM753	0.12	32	–	12	–	11
	Amoxicillin			16	–	4	–	
Pituranthos chloranthus (Pituratos green)	Tetracycline	SARM753	0.25	32	–	4	–	
	Amoxicillin			16	–	2	–	
Teucrium ramosissimum (Samosil branched)	Ofloxacin	SARM760	1	128	–	4	–	
	Oxalicin			128	–	2	–	
Melaleuca armillaris (Tea tree)	Cloxacillin	ATCC 29213	25	0.062	0.06	0.007	0.36	13
Ocimum basilicum (Fragrant basil)	Imipinem	ATCC 6538	1024	4	32	0.125	0.06	14
		M 177						
Carum carvi L (Cumin)	Ciprofloxacin	ATCC 25923	4	0.5	–	–	0.37	15
	Amoxicillin			2	–	–	0.37	
Mentha piperita (Peppermint)	Ampicillin	ATCC 6538	9.1	0.1	1.82	0.03	0.44	16
	Gentamicin	ATCC 6538	9.1	2	0.91	0.06	0.11	
		ATCC 43300	9.1	8	0.46	2.0	0.3	
Cinnamomic cassia (Chinese cinnamon)	Ampicillin	ATCC 25923	4.88	0.16	0.61	0.04	0.38	17
	Levomicetin			0.31	1.22	0.08	0.5	
Pelargonium graveolens (Pelargonium fragrant)	Ciprofloxacin	ST2	8.96	16	–	–	0.38	18
	Norfloxacin	ATCC 6532	720	0.5	–	0.6	0.37	19
Satureja montana (Mountain savory)	Gentamicin	ATCC 25923	0.78	0.5	0.19	0.06	0.36	20
		P6528	0.39	0.5	0.1	0.03	0.31	
Croton conduplicatus (Croton, cinchona tree)	Oxalicin	ATCC 25923	256	2	16	0.5	0.31	21
		ATCC 33591	512	32	32	1.0	0.09	
	Ampicillin	ATCC 25923	256	2	16	0.25	0.18	
		ATCC 33591	512	16	32	0.5	0.09	

Note: "–" date are not provided.

Synergy in the antimicrobial action of a combination of antibiotics with other biocides. Alongside essential oils, other plant-derived substances [22–30], due to the content of alkaloids, organosulfur and phenolic compounds, coumarins, and terpenes, are promising antimicrobial. Due to the diverse composition of these compounds, their mechanism of action against pathogens (including multidrug-resistant strains) includes inhibition of cell wall synthesis, inhibition of bacterial physiology, modulation of sensitivity to antibiotics, inhibition of biofilm formation, attenuation of bacterial virulence, and inhibition of efflux. These substances are also promising for use in combinations with antibiotics.

Thus, curcumin, a natural polyphenolic alkaloid obtained from *Curcuma longa Linné*, is commonly used as a seasoning and coloring agent in the food industry. However, when combined with ampicillin, ciprofloxacin, and norfloxacin, it exhibits synergistic antimicrobial activity against *Staphylococcus aureus* strains: FIC does not exceed 0.5, and the MIC of antibiotics, when mixed with curcumin, decreases from 3.9–62 μg/ml to 0.97–7.8 μg/ml (Table 2) [22].

It has been found that the plant can contain several substances with antimicrobial properties, including emodin and rhein obtained from the leaves of the *Rheum palmatum* plant. Chemically, they are anthraquinone derivatives, exhibiting a wide range of biological properties (anti-tumor, anti-inflammatory) and can be used in combination with antibiotics [23, 24]. For example, the use of emodin with ampicillin and rhein with both ampicillin and oxacillin enabled a reduction in the MIC of antibiotics against methicillin-resistant strains of *S. aureus* by 4 and 4–16 times, respectively (Table 2).

Synergistic antimicrobial activity when mixed with antibiotics has also been demonstrated for plant biocides such as luteolin, resveratrol, silymarin/silibinin, morin, polycaprol, and berberine (Table 2) [25–30].

Morin, a flavonoid of plant origin, is effective in combination with β-lactam antibiotics (ampicillin and oxacillin) as an antimicrobial agent against *S. aureus* strains, with a fractional inhibitory concentration not exceeding 0.5 (Table 2). It has been found that morin inhibits the expression of penicillin-binding protein, making resistant strains more susceptible; moreover, this natural biocide acts on the cytoplasmic membrane, causing changes in the cell as a whole [28].

Biocide polycarpol, extracted from *Cleistochlamys kirkii* (Benth) Oliv, an African medicinal plant, demonstrates similar properties. In combination with β-lactam antibiotics, polycarpol (MIC 125–250 μg/ml) exhibited a synergistic effect against *Staphylococcus aureus* strains, reducing the MIC of oxycycline from 125 μg/ml to 1.5 μg/ml and for polycarpol from 250 to 7.5 μg/ml [29].

The Tanreqing herbal complex is obtained from a mixture of plants, including Huang Qin, Jin Yin Hua, Lian Qiao, Xiong Dan, and Shan Yang Jiao, comprising over 50 different components, such as flavonoids, phenolic and bile acids, and amino acids [31]. This complex is actively used in traditional Eastern medicine for treating upper respiratory tract infections, although its metabolism and mechanism of action are not fully understood. When combined with linezolid, Tanreqing reduced the MIC from 2.5 to 1.25 μg/ml, although the fractional inhibitory concentration (FIC) (≤ 0.5) indicated only partial synergy against *S. aureus* ATCC 43300 [31].

Therefore, in addition to essential oils, other plant compounds rich in phenols, alkaloids, and terpenes are promising for combination with antibiotics in order to enhance the effect of the latter on methicillin-resistant strains of *Staphylococcus aureus*.

Synergy of antimicrobial action of a complex of antibiotics with natural biocides against gram-negative pathogens

Resistant gram-negative bacteria pose one of the challenges in modern medicine, as they are responsible for the majority of pneumonia cases, bloodstream infections (often associated with catheter use), and other types of sepsis, acquired in the intensive care unit, such as urinary tract infections [32].

In this case, the mechanism of antimicrobial resistance arises from the expression of antibiotic-inactivating enzymes and non-enzymatic pathways, which may be a result from increased intrinsic resistance due to mutations in chromosomal genes (such as increased expression of antibiotic-inactivating enzymes, efflux pumps) obtained through the transfer of mobile genetic elements (plasmids) carrying resistance genes [33].

Against the background of the increasing resistance of such pathogens, there is a growing amount of literature reporting the effective use of a combination of antibiotics

Table 2

Antibacterial activity of a mixture of plant biocides with antibiotics against *Staphylococcus aureus* strains

Plant biocide (origin)	Antibiotic	Test culture strain	MIC plant biocide, μg/ml	MIC AB, μg/ml	MIC of the components in the mixture, μg/ml			Reference
					biocide	AB	FIC	
Curcumin (polyphenolic alkaloid)	ampicillin	ATCC 25923	250	31.25	31.25	1.25	0.18	22
	ciprofloxacin	ATCC 33591	250	62.5	62.5	7.8	0.38	
		DPS-1	250	3.9	62.5	0.97	0.5	
	norfloxacin	ATCC 33591	250	250	62.5	15.6	0.31	
		DPS-1	250	31.25	31.25	0.9	0.25	
Emodin (anthraquinone derivative)	ampicillin	ATCC 25923	25	0.9	6.25	0.22	0.5	23
		ATCC 33591	25	62.5	6.25	15.6	0.5	
Rheine (anthraquinone derivative)	ampicillin	ATCC 33591	15.6	1000	0.97	250	0.31	24
		ATCC 25923	15.6	7.8	3.5	7.8	0.5	
	oxacycline	ATCC 25923	15.6	7.8	1.95	1.95	0.37	
		ATCC 33591	15.6	250	1.95	15.6	0.18	
		DPS-2	15.6	500	3.9	125	0.5	
Sibilinine (alkaloid)	ampicillin	ATCC 25923	8	2	2	0.5	0.5	25
	oxacycline	ATCC 25923	4	1024	1	256	0.5	
		ATCC 33591	4	8	1	2	0.5	
Resveratrol (antioxidant)	ampicillin	ATCC 25923	125	31.25	15.6	1.95	0.19	26
	oxacycline		125	125	15.6	7.81	0.19	
	gentamicin		125	62.5	31.2	7.8	0.38	
	ciprofloxacin		125	31.25	15.6	3.9	0.25	
		ATCC 33591	125	500	31.2	62.5	0.38	
	vancomycin	ATCC 33591	125	1.95	31.2	0.24	0.38	
		DPS-2	125	3.9	31.2	0.98	0.5	
Luteolin (polyphenolic alkaloid)	ampicillin	DPS-1	62.5	1000	3.9	62.5	0.13	27
		DPS-2	62.5	1000	3.9	62.5	0.13	
	oxacycline	ATCC 25923	62.5	62.5	3.9	3.9	0.13	
		ATCC 33591	62.5	500	3.9	31.3	0.13	
		DPS-2	62.5	500	3.9	31.3	0.13	
	gentamicin	ATCC 25923	62.5	62.5	3.9	3.9	0.13	
		ATCC 33591	62.5	62.5	3.9	3.9	0.13	
Morin (flavonoid)	ampicillin	ATCC 33591	500	1000	31.25	250	0.31	28
		DPS-1	125	15.6	7.8	3.9	0.28	
		DPS-2	250	195	62.5	0.24	0.37	
	oxacycline	DPS-4	250	500	62.5	125	0.5	
Polycarpol (flavanone)	amoxicycline	ATCC 9144	125	250	30	7.5	0.18	29
	oxacycline	ATCC 9144	125	125	30	1.5	0.11	
Berberine (alkaloid)	oxacycline	OMS 7	64	16	16	4	0.5	30
Tanreqing (mixture of flavonoids, phenolic and cholic acids, amino acids)	linezolid	ATCC 43300	4125	25	2063	1.25	0.5	31

Note: "–" date not provide.

with various plant compounds, including essential oils (Table 3), and natural biocides, aside from essential oils (Table 4).

Antimicrobial action of a mixture of antibiotics and essential oils

Due to the presence of limolene, sebinin, terpen-4-ol in the composition, the essential oil obtained from *Pituranthos chloranthus*, in addition to its activity against methicillin-resistant staphylococci (Table 1), exhibits high antimicrobial activity (MIC is 1 μg/ml), against *Escherichia coli.* When the essential oil is used in combination with antibiotics, the minimum inhibitory concentration of the amoxicycline and oxycycline was decreased from 1024 to 60 and 260 μg/ml, respectively [11].

Essential oils of basil [14] and cumin seeds [15] exhibit a synergistic effect in combination with antibiotics (Table 3) against representatives of the genus *Pseudomonas*. In this case, the fractional inhibitory concentration did not exceed 0.5, indicating a synergistic action of such a mixture.

A mixture of peppermint essential oil with antibiotics also exhibits antimicrobial activity against *Pseudomonas aeruginosa* ATCC 27853, *Escherichia* coli ATCC 25922, and *Klebsiella pneumoniae* ATCC 19833 (Table 3). In particular, the inhibitory fractional concentration of the essential oil mixture with gentamicin and/or ampicillin against gram-negative bacterial strains did not exceed 0.5, indicating a synergistic effect of these compounds [16].

The possibility of using a combination of streptomycin with cinnamon essential oil against representatives of the *Pseudomonas* and *Escherichia* is demonstrated in the study [17]. This resulted in a two-fold reduction in both the MIC of the antibiotic and the essential oil itself (Table 3). In addition to synergy, the researchers observed an indifferent effect of using a mixture of essential oil with ampicillin and chloramphenicol on the tested cultures.

The authors [18] demonstrated synergy (FIC ≤ 0.5) in the use of a combination of geranium essential oil and ciprofloxacin against isolates of *Klebsiella pneumoniae* KT2 and *Pseudomonas mirabilis* PRT3, which are the main cause of urinary tract infections.

The study [34] showed a positive effect of using coriander essential oil in combination with various antibiotics against strains of *Acinetobacter baumannii* — nosocomial pathogens resistant to most antibiotics. These strains cause the spread of nosocomial infections, primarily associated with the colonization of medical materials. In this case, the FIC values did not exceed 0.5, indicating a synergistic action of these compounds.

As seen from the data in Table 3, the use of a wide range of essential oils in combination with commercial antibiotics appears promising against representatives of the genera *Pseudomonas, Klebsiella, Escherichia coli*, and *Proteus*.

The effect of a complex of antibiotics with natural compounds other than essential oils

The synergistic action of antibiotics and natural biocides has a number of advantages compared to the use of corresponding monopreparations. Thus, some plant compounds have a direct antimicrobial effects on antibiotic-resistant bacteria and enhance the effect of antibiotics through various mechanisms: they prevent their penetration into the cell due to dysfunction of the cytoplasmic membrane [36], inhibiting efflux pumps [37] or dispersing biofilms. Moreover, such synergistic interactions between natural substances and antibiotics increases the effectiveness of the latter while simultaneously reducing their concentration.

Thus, in the case of the combination of the natural alkaloid catharanthine obtained from the plant *Catharanthus roseous* with tetracycline and streptomycin against *P. aeruginosa* MTCC-741, it was possible to reduce the minimal inhibitory concentrations of antibiotics from 1600 to 100 and 200 μg/l, respectively [38] (Table 4).

The biocide gallotannin, extracted from the plant *Terminalia chebula*, is a derivative of 1,2,6-tri-O-galloyl-β-D-glucopyranose. When combined with gentamicin, it reduces the minimum inhibitory concentration of the antibiotic against *Escherichia coli* ATCC 8139 by 4 times. In studying the MIC, the authors found that this combination inhibits efflux pumps in the uropathogenic *Escherichia coli* ATCC 8139.

Similar effects on the activity of efflux pumps were observed when the combination of natural alkaloids, varbarine and palmatine, was applied with ciprofloxacin against *Pseudomonas aeruginosa* ATCC27853 [40].

In the study [41], the effectiveness of propolis, a natural substance obtained from bees, in combination with antibiotics against pathogenic strains of *Escherichia*

Table 3

The antibacterial activity of a mixture of essential oils with antibiotics against gram-negative bacteria

Essential oil, EO (source of obtaining)	Antibiotic (AB)	Test culture	MIC EO, µg/ml	MIC AB, µg/ml	MIC of the components in the mixture, µg/ml			Reference
					EO	AB	FIC	
Pituranthos chloranthus (Pituratos green)	amoxicycline	*Escherichia coli*	1	1024	–	260	–	11
	oxacycline		1	> 1024	–	60	–	
Ocimum basilicum (Fragrant basil)	imipenem	*Pseudomonas aureginosa* 1662339	1024	4	32	0.125	0.0625	14
	ciprofloxacin			2	32	0.125	0.09	
Carum carvi L. (Cumin)	ciprofloxacin	*Pseudomonas aureginosa* ATCC 27853	16	1	–	–	0.37	15
Mentha piperita (Peppermint)	gentamicin	*Klebsiella pneumoniae* ATCC 19833	9.1	32	1	3.64	0.43	16
		Escherichia coli ATCC 25922	9.1	1	3.64	0.03	0.43	
		Pseudomonas aureginosa ATCC 27853	9.1	2	0.46	0.06	0.08	
	ampicillin		9.1	16	2.27	4	0.5	
Cinnamomic cassia (Chinese cinnamon)	streptomycin	*Escherichia coli* ATCC 25922	4.88	3.13	2.44	1.56	0.5	17
		Pseudomonas aureginosa ATCC 27853	19.53	3.13	9.77	1.56	0.5	
Pelargonium graveolens (Pelargonium fragrant)	ciprofloxacin	*Klebsiella pneumoniae* KT2	35.88	16	–	–	0.375	18
		Proteus mirabilis PRT3	17.92	16	–	–	0.5	
Coriandrum sativum L (Coriander)	chloramphenicol	*Acinetobacter baumannii* LMG 1041	4	64	–	–	0.47	34
	ciprofloxacin	*Acinetobacter baumannii* LMG 1025	1	0.125	–	–	0.28	
	gentamicin			0.25	–	–	0.25	
	tetracycline	*Acinetobacter baumannii* LMG 1041	4	1	–	–	0.185	
Trachyspermum ammi (Azhgon)	ciprofloxacin	*Pseudomonas aeruginosa* ATCC 27853	160	3	–	–	0.25	35

Note: "–" date not provide.

coli, the causative agents of cystitis and pyelonephritis, was demonstrated (Table 4). It is noteworthy that the combination of propolis with ofloxacin, ceftriaxone, and fosfomycin reduced the MIC of antibiotics from 32–128 to 2–64 μg/ml, with fractional inhibitory concentration (FIC) values not exceeding 0.5, indicating synergy.

Therefore, in addition to essential oils, there are promising natural biocides, including those of plant and animal origin, capable of reducing the effective concentrations of antibiotics against infectious agents.

Antimicrobial effect of a mixture of antibiotics with antimicrobial peptides on gram-positive and gram-negative bacteria

Antimicrobial peptides (AMPs) are considered as new promising antimicrobial agents. AMPs significantly differ in amino acid sequence and structure, but most of them are cationic and can adopt an amphipathic conformation, allowing them to easily interact with negatively charged components on the surface of bacterial cells and integrate into the lipid bilayer [42]. The primary mechanism of the antimicrobial action of AMPs is associated with their ability to alter membrane permeability and damage its structure. This process is accompanied by the leakage of vital components, ions, and metabolites. Membrane destabilization also has an additional impact on the functioning of membrane-associated protein complexes. Some AMPs are non-membranolytic and penetrate bacterial membranes without disrupting their integrity. They have intracellular targets and interfere with metabolic processes, including the synthesis of vital cellular components. The broad-spectrum multi-target action is considered one of the reasons for the effectiveness of AMPs against multidrug-resistant bacterial strains and a barrier to the development of high-level resistance to such compounds [43].

However, natural AMPs are easily degraded by proteolytic enzymes, so various approaches are being investigated to enhance AMP stability. These include the production of “constrained” peptides, cyclotides, hybrid AMPs, conjugates, and immobilized AMPs [43]. Among these methods, the conjugation of AMPs with traditional antibiotics is promising due to the potential synergistic combination, providing effective targeting and destruction of resistant pathogenic bacteria.

For example, in the study [44], the possibility of using a combination of a natural small peptide and a synthetic peptide R10 (an analogue of the human LL-37 peptide) with antibiotics to impact Gram-negative bacteria was demonstrated. It was found that both peptides in combination with antibiotics reduced the MIC of the antibiotics (Table 5). Additionally, the authors noted that the synthetic peptide R10, unlike the natural one, is more stable and exhibits antimicrobial activity against antibiotic-resistant strains of *P. aeruginosa* (including resistance to colistin) [44].

High antimicrobial activity is also inherent in another synthetic peptide, SLAP-S25, which is a undecapeptide in its structure. When using a combination of the peptide with commercial antibiotics, the values of the fractional inhibitory concentration did not exceed 0.5, indicating their synergism (Table 5). The combination of the peptide (8 mg/kg) with colistin (1 g/kg) in *in vivo* studies on a peritonitis-sepsis model was associated with an increase in mouse survival to 90%, while the use of a single dose of colistin resulted in a survival rate not exceeding 20% [45].

In the study [46], the authors identified a synergistic antimicrobial activity against *P. aeruginosa* ATCC 9027 of a complex of antibiotics (azithromycin and rifaximin) with natural peptides obtained from the crab Scylla paramamosain (sphistin — a peptide with 38 amino acids (Table 5).

Let’s note that in the works [44–46], the authors did not attempt to establish the mechanism of the antimicrobial action of the biocide mixture but only observed the presence of synergism.

However, there are several works in which, in addition to establishing synergy, the mechanisms underlying the high antimicrobial effect of the peptide and antibiotic mixture are investigated. Thus, in the work using dielectric spectroscopy, confocal microscopy, and flow cytometry, the interaction and localization of synthetic peptides T3 and T4 with the bacterial membrane of *S. aureus* ATCC 9144 were confirmed.

The peptides were found to inhibit ethidium bromide efflux, which is a substrate for many proteins involved in the efflux system. This suggested that the peptides, after interacting with the pathogen membrane, could lead to inhibition of the excretion of antibiotics, thereby reducing their effective concentrations.

Therefore, antimicrobial peptides, both natural and synthetic, are promising compounds for use in combinations with antibiotics.

Table 4

Effect on gram-negative bacteria of a complex of antibiotics with other natural biocides

Biocide	Origin of the biocide	Antibiotic (AB)	Test culture	MIC of the biocide, μg/ml	MIC of the antibiotic, μg/ml	MIC of the components in the mixture, μg/ml			Reference
						biocide	AB	FIC	
catharantin	The alkaloid is isolated from the plant *Catharanthus roseous*	tetracycline	*Pseudomonas aeruginosa* MTCC-741	400	1600	25	100	0.062	38
		streptomycin	*Pseudomonas aeruginosa* MTCC-741	400	1600	25	200	0.125	
gallotannin	1,2,6-tri-O-haloyl-b-D-glucopyranose isolated from *Terminalia chebula*	gentamicin	*Escherichia coli* ATCC 8139	12.1	1	–	0.25	–	39
barbarian	Alkaloids isolated from the roots *Berberis vulgaris*	ciprofloxacin	*Pseudomonas aeruginosa* ATCC27853	2000	512	125	128	–	40
palmatine				2000	512	250	64	–	
propolis	material obtained with the help of bees	ofloxacin	*Escherichia coli* NECS892420	256	> 32	–	8	0.16	41
			Escherichia coli NECS118564	256	> 32	–	8	0.1	
		ceftriaxone	*Escherichia coli* NECS892420	256	> 32	–	2	0.04	
			Escherichia coli NECS118564	256	> 32	–	2	0.04	
		fosfomycin	*Escherichia coli* NECS858785	256	128	–	64	0.25	

Note: "–" date not provide.

The antimicrobial activity of the combination of surfactants and antibiotics

Since the publication of the review [12], only a few studies [48–50] have been found in the available literature regarding the potential use of microbial surfactants in combination with antibiotics. Only one study determined the value of the minimum inhibitory concentration, while others focused on the impact of the surfactant-antibiotic complex on biofilms.

Thus, in work [48], a synergistic antimicrobial effect on Gram-negative and Gram-positive bacteria was established for a combination of tetracycline with surfactants synthesized by *Staphylococcus haemolyticus* strains (Table 6). When using a surfactant complex with an antibiotic, a decrease in the MIC of the latter was observed against to the majority of the test cultures studied (with the exception of *S. aureus* ATCC 29213 and *E. coli* ATCC 25922, for which the MIC in the combination with the surfactant remained unchanged).

Researchers [49] found that under the influence of a combination of synthesized sophorolipids from *Candida bombicola* ATCC 22214 (300 μg/ml) and tetracycline (15 μg/ml), complete growth inhibition of *S. aureus* ATCC 29737 was observed within 4 h, while a similar result was achieved using monopreparations of surfactants and antibiotics at higher concentrations (400 and 300 μg/ml, respectively).

In the study [50], the possibility of using a combination of lipopeptide synthesized by *Bacillus licheniformis* V9T14 at a concentration of 5 μg/ml and ampicillin (2 μg/ml) to disrupt the biofilm of *E. coli* CFT073 was demonstrated, with a 76% degree of biofilm disruption observed due to the action of such a mixture. It should be noted that the monocompounds of both the lipopeptide and the antibiotic at the mentioned concentrations did not inhibit the growth of the biofilm.

Table 5

Synergistic antibacterial effect of a mixture of peptides and antibiotics

Peptide	The origin of the peptide	Antibiotic (AB)	Test culture	MIC of the peptide, μg/ml	MIC of the antibiotic, μg/ml	MIC of the components in the mixture, μg/ml			Reference
						peptide	AB	FIC	
Nizin	*Lactococcus lactis*	tobramycin	*Acinetobacter baumannii* ATCC 19606	128	64	16	16	0.5	44
			Acinetobacter baumannii XDR 5	64	2	16	0.5	0.5	
		ciprofloxacin	*Pseudomonas aeruginosa* col 2	128	4	32	1	0.5	
P10	Chemically synthesized	ceftazidime	*Acinetobacter baumannii* ATCC 19606	4	4	1	1	0.5	
			Pseudomonas aeruginosa col 2	8	32	2	4	0.5	
SLAP–S25	Chemically synthesized	rifampicin	*Escherichia coli* B2	4	128	–	–	0.031	45
		tetracycline		4	128	–	–	0.281	
		vancomycin		4	128	–	–	0.094	
Sphistin	Derived from crab *Scylla paramamosain*	azithromycin	*Pseudomonas aeruginosa* ATCC 9027	24	180	–	–	0.35	46
		rifampicin			2.5	–	–	0.312	
$Sph_{12–38}$		azithromycin		12	180	–	–	0.225	
		rifampicin			2.5	–	–	0.375	
T3	Chemically synthesized	ampicillin	*Staphylococcus aureus* ATCC 9144	307	1	38	0.125	0.25	47
		oxacycline				38	0.125	0.25	
T4		ampicillin		331		83	0.125	0.38	
		oxacycline				83	0.125	0.38	
melimine	Chemically synthesized	ciprofloxacin	*Pseudomonas aeruginosa* 6294	250	1	–	–	0.5	48
Mel4				250	1	–	–	0.5	

Note: "–" date not provide.

Table 6

Effect on gram-positive and gram-negative bacteria of the surfactant complex *Staphylococcus haemolyticus* with tetracycline (AB) [48]

Surfactant, producer	Test culture	MIC Surfactant, μg/ml	MIC AB, μg/ml	MIC AB in the mixture, μg/ml
BS29 *Staphylococcus haemolyticus* MD29	*Pseudomonas aeruginosa* ATCC 23853	12.5	0.76	0.006
	Staphylococcus epidermidis ATCC 3598412	25	0.048	0.048
	Enterococcus faecium ATCC 19434	25	0.76	0.048
	Staphylococcus aureus ATCC 29213	25	0.76	0.76
	Escherichia coli ATCC 25922	> 25	0.76	0.76
	Klebsiella pneumoniae ATCC 700603	> 25	31	6.1
BS49 *Staphylococcus haemolyticus* MD49	*Pseudomonas aeruginosa* ATCC 23853	6.25	0.76	0.76
	Staphylococcus epidermidis ATCC 3598412	> 25	0.048	0.048
	Enterococcus faecium ATCC 19434	> 25	0.76	0.048
	Staphylococcus aureus ATCC 29213	> 25	0.76	0.76
	Escherichia coli ATCC 25922	> 25	0.76	0.76

Note: "— " date not provide.

Conclusions

Analysis of the literature data on the synergistic antimicrobial effects of a combination of antibiotics with various biocides (Tables 1–6) allows us to conclude that:

1) The majority of the available literature works on synergistic effects are related to the study of the possibility of using antibiotics specifically with essential oils. This is due to the high antimicrobial activity of certain preparations of essential oils, the ability of their main components (terpenes, phenols, alcohols, etc.) to cause damage to the cell membrane, leading to extravasation of intracellular contents and a broad spectrum of action, including against resistant microorganisms.

2) Natural compounds, in addition to essential oils, which chemically include alkaloids, phenols containing coumarins and terpenes, are also promising antimicrobial agents. In combination with antibiotics, they can inhibit the synthesis of the cell wall and modulate sensitivity to antibiotics.

3) The use of antimicrobial peptides (both natural and synthetic) in combination with antibiotics allows for increasing the resistance of peptides to the action of proteolytic enzymes and reducing the effective concentration of antibiotics.

4) There is a limited number of studies in the literature regarding the potential use of antibiotics in combination with microbial biosurfactants. Moreover, in existing works, the researchers only established the fact of a reduction in the concentration of antibiotics in the complex, without calculating the inhibitory fractional concentration. We assume that the limited research on the synergistic antimicrobial effects of antibiotics with such microbial metabolites is due to the dependence of the biological properties of the latter on the cultivation conditions of the producers.

Nevertheless, despite a considerable number of works, the exploration of the mechanisms underlying the synergistic action of compounds in the complex remains promising, which will broaden the spectrum of their applications.

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СИНЕРГІЗМ АНТИМІКРОБНОЇ АКТИВНОСТІ АКТИБІОТИКІВ З БІОЦИДАМИ ПРИРОДНОГО ПОХОДЖЕННЯ

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На сьогодні антибіотикотерапія залишається основним методом лікування інфекційних захворювань людей. Тим не менш, її ефективність стрімко знижується на тлі швидкого поширення резистентних збудників, що зумовлює пошук нових напрямів, серед яких можливість використання антибіотиків у комбінації з іншими природними сполуками.

Мета огляду — узагальнити наявні у літературі дані щодо синергізму антимікробної дії суміші антибіотиків із різноманітними біоцидами щодо грампозививних та гарамнегативних патогенних мікроорганізмів.

Аналіз даних літератури показав, що перспективними сполуками, які можуть бути використані у сумішах з антибіотиками, є ефірні олії, відмінні від ефірних олій рослинні компоненти, антимікробні пептиди (в тому числі як природного, так і синтетичного походження) та мікробні поверхнево-активні речовини. У більшості робіт дослідники розраховували показник фракціної інгібувальної концентрації, що підтверджував синергізм антимікробної активності антибіотиків та вищенаведених сполук.

Використання природних біоцидів у суміші з комерційними антибіотиками, щодо грамнегативних (зокрема метицилінрезистентних) представників роду *Staphylococcus* та грампозитивних мікроорганізмів (*Escherichia coli, Pseudomonas aureginosa, Klebsiella pneumoniae, Proteus mirabilis*, *Acinetobacter baumannii*) дає змогу розглядати такі суміші не лише як ефективні антимікробні агенти, а й як один зі шляхів зменшення ефективної концентрації антибіотиків.

Варто зазначити, що у представлених роботах дослідники лише констатують факт синергізму антимікробної активності комплексу антибіотиків та інших біоцидів, не акцентуючи увагу на можливих механізмах взаємодії компонентів комплексу, які, ймовірно, залежать від багатьох факторів, зокрема, якісного складу природних сполук. Тому важливим є продовження досліджень не лише синергізму антимікробниї активності сумішей сполук, а й механізмів, що лежать в основі їх взаємодії, що дасть змогу підвищити їхню ефективність у боротьбі з резистентними мікроорганізмами.

Ключові слова: антимікробна дія, патогенні мікроорганізми, фракційна інгібуювальна концентрація.