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SYNERGISTIC ACTION ON MICROORGANISMS OF COMPLEX OF ESSENTIAL OILS WITH THE BIOCIDES

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This review summarizes the published data and own results concerning synergism of antimicrobial activity of essential oils with antibiotics against bacteria of the family *Enterobacteriaceae*, genera *Staphylococcus, Pseudomonas, Acinetobacter*; with synthetic antifungal drug fluconazole, against yeast genus *Candida*; with surfactants of microbial origin, against bacterial and yeast test cultures. The synergistic effect of the complex of essential oils with antibiotics, enzymes, surfactants, etc. on biofilms was considered as well. Mixing essential oils with other biocides allowed to significantly decrease the minimum inhibitory concentrations of each component. The probability of emerging resistance to antibiotics was also reduced in the pathogenic bacteria and yeasts due to the antimicrobial action of essential oils that caused the dysfunction of cellular membrane of microorganisms. The prospects of implementing complex essential oils with antibiotic nisin in the food industry, and with other antibiotics in veterinary medicine are discussed.

Key words: essential oils, antimicrobial compounds, synergism of antimicrobial action, destruction of biofilms.

According to recent studies of World Health Organization (WHO), almost half of clinical isolates of methicillin resistant strains of *Klebsiella pneumoniae* and *Staphylococcus aureus*, and of *Escherichia coli* are resistant to 3rd generation cephalosporins, fluoroquinolones and carbapenems [1]. Likewise, the resistance of representatives of the genus *Candida* is increasingly reported against fluconazole (93%), amphotericin B (35%) and echinocandins (7%) [2]. Those pathogens annually cause illnesses of nearly 700 thousand people worldwide, and according to some experts those numbers may reach 10 billion as early as 2050 [3].

Reducing the number of antibiotic-resistant microorganisms can be achieved by using alternative compounds of natural origin, such as bacteriocins, microbial peptides, surfactants (SA) [4, 5] and essential oils (EO) [6–8]. The latter contain aldehydes, alcohols and phenolic compounds and thus are effective antimicrobial agents. That is why EO can be used instead of antibiotics and synthetic compounds in the cosmetic, food and pharmaceutical industries. However, the minimum inhibitory concentrations (MIC) of EO are rather high (400–1600 μg/ml) [6–8], leading to high EO content in the various products. Simultaneously, EO in such concentrations are known to cause severe damage to the central nervous system, and aspiration pneumonia [9]. The concentration of EO can be reduced without affecting their properties if they are used in combination with other biocides.

The present review is aimed to analyze and summarize the published data on the synergic antimicrobial activity of essential oils and other antimicrobial compounds, and on their synergic activity on biofilms.

Synergistic antimicrobial activity of essential oils and antibiotics

First data on using the mixtures of EO and antibiotics was published in 1978 [10]. Since then, each year new reports are presented of the synergistic activity of those antimicrobial compounds [6, 8, 11–17]. There are several reasons for that. Firstly, the nature of antimicrobial activity of EO lies in destabilizing the phospholipid layer of the cellular membrane, disabling its functions [18]. Thus, the probability of microbial resistance to EO is virtually absent. Secondly, in the presence of EO, antibiotic quickly enters the microbial cell, preceding the activation of pathogenic resistance, and therefore is not ejected or deactivated. That also reduces the probability of microbial resistance emerging, and the effective concentration of antibiotic [11–14]. According to the publications, the antimicrobial activity of EO depends firstly on their qualitative content, which changes seasonally and is not equal in all plant parts from which EO are obtained [6, 8, 11–17].

It should be noted that in most works, the pathogens most frequently used as a test culture to determine antimicrobial activity are the bacteria of the family *Enterobacteriaceae* [6, 11–16, 19], the genus *Staphylococcus* [6, 8, 17] and yeast *Candida* [20–23].

They are usually chosen because enterobacteria are the main agents of diseases of the gastrointestinal tract and can contaminate the surfaces of food industry equipment and medical equipment. That is why searching for modern antimicrobials that are effective against members of this family remains the priority [6, 11–16, 19]. The bacteria of the genus *Staphylococcus* also are well-known pathogens, which cause purulent inflammation of the skin, bones and organs in humans and animals, and are characterized by increased resistance to a wide range of antibiotics [6, 8, 17]. Therefore, it is important to look for compounds, alternative to antibiotics, with high antimicrobial activity, in particular, against the resistant strains of *Staphylococcus aureus*.

Candida yeast is capable of causing serious infectious diseases (candidiasis), and the number of drugs for treating such infections is limited by the rapid appearance of antibiotic-resistant strains [20–23].

Methods for evaluation of synergism of antimicrobial action. In most publications [7, 11–13], antimicrobial activity of EO, antibiotics and their mixtures was analyzed by the indexes of minimum inhibitory concentrations (MIC). The synergism of antimicrobial activity was assessed by firstly determining MIC for each compound separately. MIC of a mixture was determined using the EO and antibiotic solutions with concentrations twice lower than MIC of each monopreparation, with the ratio of antimicrobial solutions of 1: 1. In one version of experiment, the concentration of antibiotic in mixture remained the same, while that of EO was reduced by serial two-fold dilutions. Conversely, in another version of experiment, concentration of EO was the same, and that of antibiotic was reduced.

In several publications [6–8, 11–14, 17] the synergism of antimicrobial activity was studied using the fractional inhibitory concentration index (FIC):

$$FIC = (CA/MICA) + (CB/MICB),$$

where: CA, B — concentration of antimicrobial compound A and B in mixture;

MICA,B — minimum inhibitory concentration of antimicrobial compound A and B.

FIC index values ≤ 0.5 indicates the synergistic activity of two antimicrobial compounds.

Antimicrobial activity of mixture of essential oils and antibiotics against the representatives of the family Enterobacteriaceae. Due to the presence of lipopolysaccharides Gram-negative bacteria are more resistant to EO than gram-positive ones which have cell walls more permeable to phenolic compounds (eugenol, thymol, carvacrol) and aldehydes (citral, citronellal, cinnamaldehyde) [24].

In [6], it was found that, for mixtures of amoxicillin with EO of Mediterranean aster, antibiotic MIC against the strains of gram-negative bacteria *Enterobacter cloacae*, *Salmonella* sp. and *Escherichia coli* were 4–8 times lower than those for each compound separately (Table 1).

The MIC of neomycin against *E. coli* was 32 μg/ml, and in the mixture with EO of the Mediterranean aster it decreased to 8 μg/ml.

Fadli et al. [11] established the synergistic antimicrobial activity of a macrolide antibiotic pristinamycin and EO of *Thymus maroccanus* against the strains of *E. cloacae* and *E. coli*. Using a mixture of pristinamycin with EO lead to a decrease in the MIC of both antibiotics and EO. Thus, MIC of EO against the test cultures were reduced by 4–8 times, and those of pristinamycin were lower by 2–3 orders of magnitude compared to the MIC values for individual compounds (Table 1).

Table 1. **Antibacterial activity of mixture of essential oils and antibiotics against representatives of the family *Enterobacteriaceae***

Essential oil	Antibiotic	Test culture	MIC of essential oil, μg/ml	MIC of antibiotic, μg/ml	MIC of components in mixture, μg/ml			References
					essential oil	antibiotic	FIC	
Cladanthus arabicus	Amoxicillin	*Enterobacter cloacae* (S5/16)	800	64	–	8	0.13	[6]
		Salmonella sp. (S12/14)	400	64	–	16	0.29	
		Escherichia coli ATCC 25922	800	64	–	8	0.13	
Thymus maroccanus	Pristinamycin	*Enterobacter cloacae*	342	250	–	–	0.5	[11]
		Escherichia coli	342	125	–	–	0.5	
Satureja montana	Gentamicin	*Escherichia coli* ATCC 25922	1560	1.0	390	60	0.31	[12]
		Escherichia coli PG19	3120	4.0	780	1.0	0.5	
		Escherichia coli PG32	1560	1.0	390	0.125	0.37	
	Chloramphenicol	*Escherichia coli* TEM-1	–	–	–	–	0.32	[14]
	Tetracycline		–	–	–	–	0.21	
Lavandula	Piperacillin	*Escherichia coli* J53 R1	4% (v/v)	1024	0.5% (v/v)	128	0.26	[13]
Cinnamon			0.078% (v/v)	1024	0.02% (v/v)	256	0.5	
Mentha piperita	Meropenem	*Escherichia coli* J53 pMG309	8% (v/v)	4	1% (v/v)	0.50	0.26	

Note: "–" data not present.

Using mixture of EO of *Satureja montana* with gentamicin against various strains of *E. coli* also lead to lower MIC of antibiotic and EO [12]. Yap et al. [13] showed that using mixtures cinnamon and lavender EO with piperacillin, or meropenem with peppermint EO against *E. coli* reduced MIC in 4–8 times. In that case FIC was lower than 0.5, supporting the synergistic nature of antimicrobial activity (Table 1).

Mixture of thyme EO with tetracycline and chloramphenicol was also shown to have synergistic activity against *E. coli* (FIC of 0.32 and 0.21, respectively) [13].

Authors of [15] studied the synergistic activity of cumin EO and ciprofloxacin against *Shigella flexneri*, Gram-negative bacteria which penetrate the epithelium of the colon and cause its ulcer. The established MIC of antibiotic and EO were 0.4 mg/l and 150 μl/l respectively. Complete inhibition of *S. flexneri* growth was observed when a mixture of cumin EO and ciprofloxacin was used in concentrations equivalent to their MIC. Further studies were performed on experimental rats, and that mixture was shown to have a synergistic effect, which was accompanied by a decrease in inflammation of the mucous membrane and healing in the epithelial lining of the colons of rats, pre-infected with *S. flexneri*.

Talei et al. [16] showed the possibility to reduce MIC of ciprofloxacin and vancomycin by 2–4 times (to 0.12–0.16 μg/ml) against the nosocomial isolates of *E. coli* in the presence of ajowan caraway EO. The authors suggest that

using this mixture in medical practice will reduce the risk of diseases caused by *E. coli*, and prevent the development of resistance of these microorganisms to known antibiotics. Notably, in [15, 16] the authors did not establish a FIC, but only analyzed the decrease in effective MIC when added essential oils to the antibiotics.

Another common pathogen that causes severe nosocomial infectious diseases is *Klebsiella pneumoniae*. The multi-resistant *K. pneumoniae* strains quickly become tolerant to known antibiotics, which significantly complicates the treatment of the relevant diseases. In order to prevent the development of resistance, scientists from Egypt [19] investigated the possible synergism of the antimicrobial activity of a mixture of ciprofloxacin and peppermint and cumin EO against different strains of *K. pneumoniae*. Adding EO to the antibiotic (at a concentration equivalent to MIC) was accompanied by a decrease in the latter's MIC by 2–4 times (Table 2).

Hence, the data given in Tables 1 and 2 indicate the possibility of reducing both the concentration of antibiotics and essential oils in the case of using their mixture as antimicrobial agents against members of the family *Enterobacteriaceae*.

Synergistic antimicrobial activity of essential oils and antibiotics against the representatives of the genus Staphylococcus and other bacteria. In [17] it was established that using a mixture of the antibiotic cloxacillin and tea tree EO allowed reducing the MIC of each of the antimicrobials against different penicillin-resistant strains of *S. aureus* (Table 3). In that case though, FIC value was > 0.5, thus there was no synergistic activity of the mixture components. Despite that the authors claim that combining cloxacillin with EO allowed reducing the MIC of antibiotic and preventing the emergence of resistance to it in the studied pathogen.

Scientists from Brazil [7] have determined the synergistic antimicrobial activity of imipenem and fragrant basil EO against the main pathogens of purulent infections, *S. aureus* and *Pseudomonas aeruginosa*. MIC of that antibiotic in mixture with EO against *S. aureus* ATCC 6538, *S. aureus* M-177 and *P. aeruginosa* 1662339 decreased by several times compared with those for the not-mixed antibiotic (Table 3).

Synergistic antimicrobial activity against *S. aureus* strains was also observed for a mixture of ajowan caraway EO with ciprofloxacin and amoxicillin, as well as with amoxicillin against *P. aeruginosa* [8]. In that study, the FIC index did not exceed 0.5 (Table 3).

The synergistic effect of coriander EO and antibiotics chloramphenicol, ciprofloxacin, gentamicin was established against the nosocomial isolates of Gram-negative *Acinetobacter baumannii* bacteria, resistant to a wide range of antibiotics [10]. This conclusion is based on the determination of FIC, which was less than 0.5 (Table 3).

Table 2. **Effect of complex of peppermint and cumin essential oils, and ciprofloxacin on several strains of *Klebsiella pneumoniae* [19]**

Essential oil	Strains of *K. pneumoniae*	MIC of ciprofloxacin, μg/ml	MIC of essential oil,% (v/v)	MIC of ciprofloxacin in mixture, μg/ml
Peppermint	КР1	16	4	8
	КР3	16	4	8
	КР5	32	4	16
	КР7	64	4	32
	КР8	16	4	8
Cumin	КР1	16	4	4
	КР3	16	0.25	8
	КР5	32	4	8
	КР7	64	1	8
	КР8	16	4	4

Scientists from Thailand [25] have shown that using tetracycline in combination with ginger EO has a high antimicrobial effect on *A. baumannii* bacteria, resistant to a broad spectrum of antibiotics. For example, using individual preparations of tetracycline or ginger EO at a concentration of 7 mg/ml growth resulted in 25 and 14 mm inhibition zone of *A. baumannii*, respectively. If test substances of the same concentrations were mixed in a 1:1 ratio, the growth inhibition zone increased to 46.5 mm. It should be noted that this is the first work in which the possibility has been established of using ginger EO in medical practice to control multi-resistant strains of microorganisms.

Table 3. **Antibacterial activity of mixture of essential oils and antibiotics against representatives of the genera *Staphylococcus*, *Pseudomonas* and *Acinetobacter***

Essential oil	Antibiotic	Test culture	MIC of essential oil, μg/ml	MIC of antibiotic, μg/ml	MIC of components in mixture, μg/ml			References
					essential oil	antibiotic	FIC	
Tea tree	Cloxacillin	*Staphylococcus aureus* ATCC 29213	25	0.125	25	0.031	0.75	[17]
		Staphylococcus aureus 13	12.5	0.5	6.25	0.125	0.62	
		Staphylococcus aureus 139	12.5	0.5	6.25	0.125	0.62	
		Staphylococcus aureus 96	12.5	0.5	6.25	0.125	0.62	
Basil	Imipenem	*Staphylococcus aureus* ATCC 6538	1024	4	32	0.125	0.062	[7]
		Staphylococcus aureus M-177	1024	4	32	0.125	0.062	
		Pseudomonas aeruginosa 1662339	1024	4	32	0.125	0.062	
Ajowan caraway	Amoxicillin	*Staphylococcus aureus* MRSA 37	800	2	–	–	0.36	
	Ciprofloxacin		800	4	–	–	0.35	[8]
	Ciprofloxacin	*Pseudomonas aeruginosa* ATCC 27853	1600	4	–	–	0.37	
Coryiander	Chloramphenicol	*Acinetobacter baumannii* LMG 1025	0.1% (v/v)	32	–	–	0.312	[10]
		Acinetobacter baumannii LMG 1041	0.4% (v/v)	64	–	–	0.047	
	Ciprofloxacin	*Acinetobacter baumannii* LMG 1025	0.1% (v/v)	0.125	–	–	0.281	
		Acinetobacter baumannii LMG 1041	0.4% (v/v)	0.25	–	–	0.375	
	Gentamicin	*Acinetobacter baumannii* LMG 1025	0.1% (v/v)	0.25	–	–	0.250	
		Acinetobacter baumannii LMG 1041	0.4% (v/v)	8	–	–	0.375	

Note: «–» data not presented.

In [26], the authors established the synergistic antimicrobial activity of a complex of cumin EO and ciprofloxacin against the main agents of respiratory diseases (pneumonia, sinusitis, meningitis, etc.), ciprofloxacin-resistant strains of *Streptococcus pneumoniae*, as evidenced by FIC values lower than 0.5 (Table 4).

Therefore, the use of antibiotics in combination with essential oils is effective to increase antibacterial activity against pathogenic strains of the genera *Staphylococcus, Pseudomonas* and *Acinetobacter*.

Effect of mixture of essential oils and fluconazole on yeasts of the genus *Candida*

There are reports [20–23] about significantly reduced MIC of synthetic antifungal preparation fluconazole in presence of various essential oils.

In [20] it was determined that MIC of fluconazole, linalool and gerandiol (two main components of basil EO) against fluconazole-resistant yeast *Candida albicans* were 500, 1580 and 152 μg/ml, respectively. Adding linalool and gerandiol to fluconazole caused significant reduction of MIC of all components (Table 5).

Interestingly, MIC were reduced in mixtures of EO with antibiotic, and in mixtures of linalool and gerandiol.

Scientists from Brazil [21] found the synergistic antimicrobial activity of guava EO and fluconazole against representatives of the genus *Candida*, and the antimicrobial activity of EO depended on the season of the year. Thus, minimum fungicidal concentration (MFC) of fluconazole against *C. albicans* INCQS 40006 was 8.192 μg/ml. Adding EO extracted from guava in February to fluconazole (1: 1) reduced MFC to 1.024 μg/ml, while adding EO obtained in August only halved it. Similar results were obtained for *C. krusei* INCQS 40095: MFC of fluconazole was ≥ 16.384 μg/ml and decreased twofold in combination with EO obtained in August, and was reduced to 1.024 μg/ml using EO collected in May. It should be noted that in that work the authors did not try to find out the reasons for the dependence of the antimicrobial activity of oil on the season.

Morais-Braga et al. [22] have also investigated the synergistic interaction of fluconazole and guava EO. In studies, they used EO of two different varieties of guava: *Psidium guajava* and *Psidium brownianum*. Antimicrobial activity was assessed by IC_{50}, concentration of substance (μg/ml), which causes the death of 50% of cells. *C. albicans* INCQS 40006, *C. albicans* LM 77, *C. tropicalis* INCQS 40042 and *C. tropicalis* LM 23 were used as test cultures (Table 6).

The data in Table 6 show that the IC_{50} determined for the mixture of antifungal preparation and the studied guava EO was significantly lower than IC_{50} of fluconazole, which indicates their synergistic effect.

The antifungal effect of fluconazole and peppermint EO on fluconazole-resistant yeast of the genus *Candida* was investigated in [23]. It was found that MIC of each component individually were several times higher than their MIC in the mixture (Table 7). The FIC index did not exceed 0.5, which indicates the synergism of antimicrobial activity of antifungal preparation and essential oil.

Thus, the few available reports on the synergism of the antimicrobial activity of a mixture of essential oils with antibiotics and synthetic antifungal drugs (such as fluconazole) indicate the possibility of reducing the concentration of antibiotics for the treatment of various infectious diseases without inducing resistance in the pathogens.

Table 4. **Synergistic activity of complex of cumin essential oil and ciprofloxacin against strains of *Streptococcus pneumoniae* [26]**

Streptococcus pneumoniae strain	MIC of essential oil, μg/ml	MIC of ciprofloxacin, μg/ml	FIC
1	0.625	5	0.37
2	1.25	5	0.14
3	2.5	10	0.14
4	1.25	10	0.22
5	1.25	5	0.37
6	0.625	2.5	0.37
7	0.625	5	0.37

Table 5. **Antifungal activity of fluconazole, linalool and gerandiol against *Candida albicans* [20]**

Antimicrobial substance	MIC in mixture, μg/ml	FIC
Linalool	197	0.134*
Fluconazole	2.02	
Gerandiol	38	0.252**
Fluconazole	1.04	
Linalool	397	0.284***
Gerandiol	4.8	

Note: * — FIC of mixture of linalool and fluconazole; ** — FIC of mixture of gerandiol and fluconazole; *** — FIC of mixture of linalool and gerandiol.

Table 6. **Antimicrobial activity of mixture of fluconazole and guava essential oils against yeasts of the genus *Candida* [22]**

Antimicrobial substance	Test culture	IC_{50} (μg/ml)
Fluconazole	*Candida albicans* INCQS 40006	19.22
	Candida albicans LM 77	32.41
	Candida tropicalis INCQS 40042	68.10
	Candida tropicalis LM 23	41.11
Fluconazole and EO of *Psidium guajava*	*Candida albicans* INCQS 40006	8.77
	Candida albicans LM 77	3.82
	Candida tropicalis INCQS 40042	15.24
	Candida tropicalis LM 23	12.68
Fluconazole and EO of *Psidium brownianum*	*Candida albicans* INCQS 40006	8.30
	Candida albicans LM 77	3.78
	Candida tropicalis INCQS 40042	3.10
	Candida tropicalis LM 23	10.20

Table 7. **Synergistic antifungal activity of peppermint essential oil and fluconazole on yeasts of the genus *Candida* [23]**

Test culture	MIC of essential oil, μg/ml	MIC of fluconazole, μg/ml	MIC of components in mixture		FIC
			oil, mg/ml	fluconazole, μg/ml	
C. albicans ATCC 10231	2.28	1.0	0.91	0.06	0.46
C. glabrata ATCC 15126	1.14	16.0	0.46	0.1	0.47
C. krusei ATCC 6258	4.54	16.0	1.82	1.0	0.46
C. kefyr ATCC 204093	4.54	2.28	1.82	0.25	0.46

Antimicrobial activity of mixture of surfactants and essential oils

It should be noted that the information is extremely limited on the synergism of the antimicrobial activity of EO with microbial surfactants. In 2014, Haba et al. [27] found that rhamnolipids synthesized by *P. aeruginosa* 47T2 in an emulsion with EO of tea tree, lavender, oregano and cinnamon show an antimicrobial effect against *S. aureus* ATCC 43300 and *C. albicans* ATCC 10231. Thus, emultion of water: rhamnolipids: tea tree EO in ratio (%) 71.8: 2.8: 25.3 inhibited the growth of methicillin-resistant strain *S. aureus* ATCC 43300. The growth inhibition zone was 15.2 mm, while under the effect of essential oil or rhamnolipids separately, it was 11 and 9 mm, respectively. More effective antimicrobial agents were emulsions (%) of water: rhamnolipids: oregano EO (72.2: 11.1: 16.7) and water: rhamnolipids: cinnamon EO (80.9: 1.9: 17.1): the inhibition zones for *C. albicans* ATCC 10231 were 39.3 and 36.0 mm, respectively. Interestingly, rhamnolipids at a concentration of 1.9% (effective concentration of rhamnolids in the composition of an emulsion with cinnamon EO) did not inhibit the growth of *C. albicans* ATCC 10231 at all. The authors note that rhamnolipids are effective emulsifying agents that, by dispersing essential oils, increase their antimicrobial activity.

Our own studies [28] have shown that, with the simultaneous introduction of emulsions based on tea tree oil (12.5 µl/ml) and surfactant (0.43 mg/ml) to the suspension of test cultures of *C. albicans* D-6, *Aspergillus niger* P-3, and *S. aureus* BMS-1 (104–105 cells/ml), the number of living cells after 15 min of exposure was 0.7% to 66% lower than if the microbial suspension were treated with oil preparations without surfactants.

In the following studies, we established a synergism of the antimicrobial activity of tea tree EO and surfactants of *Nocardia vaccinii* IMV B-7405 against *Pseudomonas* sp. MI-2, *S. aureus* BMS-1, *E. coli* IEM-1 and *B. subtilis* BT-2. MIC of essential oil in the test cultures were 625–156 µg/ml, and in the presence of surfactants they decreased by 2 to 260 times. MIC of the mixtures of EO and surfactant were three orders of magnitude lower against *S. aureus* BMS-1 and *B. subtilis* BT-2 than MIC established for essential oil only.

Further experiments showed that surfactants of *N. vaccinii* IMV B-7405 exhibited a synergistic effect when mixed with cinnamon and lemongrass EO. Thus, MIC of EO against *C. albicans* D-6, *C. tropicalis* PE-2 and *C. utilis* BMS-65 were in the range of 312–156 µg/ml, and if EO were added to the surfactant solution, their MIC decreased to 9.7–39 µg/ml.

Therefore, our own studies are among the first few to demonstrate the synergistic antimicrobial activity of essential oils with microbial surfactants.

The role of mixture of essential oils with other preparations in degradation of biofilms

In addition to antimicrobial activity, essential oils have the ability to degrade biofilms [29–31]. The mechanism of biofilm degradation under the activity of EO is associated with the presence of phenolic terpenoids (thymol, carvacrol) in their composition. The terpenoids can penetrate the polysaccharide matrix and cause antimicrobial action. Due to their hydrophobic nature, EO interact with the bilipid layer of the cytoplasmic membrane, causing it to lose integrity and hence impairing its function [32, 33].

The need of new compounds capable of destroying biofilms is primarily due to the fact that microorganisms in the biofilm have increased resistance to known biocides and rapidly acquire that resistance [33–36].

The available literature on the use of a mixture of essential oils with other antimicrobial compounds for the degradation of biofilms relates mainly to the complex of EO with antibiotics [34, 36, 37] or fluconazole [35].

Thus, in [33] it was found that using mixture of certain components of EO with streptomycin increased the degradation of the biofilms of *Salmonella typhimurium* SL1344 and *Listeria monocytogenes* CMCC 54004. The authors used cinnamaldehyde, eugenol, and thymol as EO components of cinnamon, clove and thyme, respectively. For example, applying a mixture of streptomycin with cinnamaldehyde (32 µg/ml) caused 56% degradation of the *S. typhimurium* CMCC 54004 biofilm, and at a higher concentration of the components in the mixture (128 µg/ml), 85% degradation of *S. typhimurium* SL1344 biofilm. It should be noted that the degree of biofilm degradation for the strains SL1344 and CMCC 54004 treated with streptomycin alone at concentrations of 1 and 2 µg/ml, respectively, did not exceed 20%.

Budzyn´ska et al. [34] showed that treatment with mupirocin (32 µg/ml) caused 14% degradation of the combined biofilm of *C. albicans* ATCC 10231 and *S. aureus*

NCTC 8325-4, and with the addition of clove EO at the same concentration (1:1 ratio) it increased to 58.06%. The authors in the same work investigated the degree of the biofilm degradation in the presence of a mixture of clove oil with fluconazole. If only antifungal drug (64 μg/ml) were used, the observed degradation of the combined biofilm was only by 6.05%. Adding clove EO in the same concentration was accompanied by an increase in the degree of degradation to 61.11%.

In [35], it was found that thymol, eugenol and carvacrol (the main antimicrobial components of cumin EO) exhibited synergistic effects with tetracycline against pathogens of oral cavity diseases. The authors showed that the *S. aureus* B193 biofilm was degraded by 50% with tetracycline at a concentration of 12 μg/ml and eugenol, carvacol and thymol at 250, 79 and 85 μg/ml, respectively. Mixing tetracycline with these antimicrobial compounds (at a concentration twice their MIC) caused the same degree of biofilm degradation at a much lower concentration (6 μg/ml for eugenol and carvacol, 9 μg/ml for thymol). Similar results were observed for the degradation of biofilm for other representatives of the genus *Staphylococcus* (Table 8).

Indian scientists have found that *p*-coumaric acid (a major component of black cumin EO) has synergistic activity with nisin in the degradation of biofilms of the major food pathogens *Bacillus cereus* MTCC 1272 and *S. typhimurium* MTCC 3224 [36]. Thus, nisin at a concentration of 0.013 mg/ml destroyed the biofilm of *B. cereus* MTCC 1272 by 23–27%, and that of *S. typhimurium* MTCC 3224 by 12–15% at a higher concentration (0.208 mg/ml). When *p*-coumaric acid (0.041 mg/ml) was added, the biofilm degradation of strain MTCC 1272 increased to 90%. The same degree of biofilm degradation of strain MTCC 3224 was achieved by introducing *p*-coumaric acid at a higher concentration (0.104 mg/ml).

In the same work [36], the authors established a synergistic effect of linalool (a major component of coriander EO) and nisin in the degradation of the biofilms of *B. cereus* MTCC 1272 and *S. typhimurium* MTCC 3224. When linalool was added to the nisin, the degradation of these biofilms increased 3–4 times (up to 65–80%) compared to the antibiotic alone.

Nuryastuti et al. [37] showed that cinnamon EO at a concentration of 2% (v/v) in 24 h completely degraded biofilms of various *Staphylococcus epidermidis* strains that colonize medical equipment and apparatus.

Farisa Banu et al. [38] established a synergistic effect of cinnamon oil with the enzyme preparation of deoxyribonuclease I (DNAase I). In the presence of only cinnamon oil at a concentration of 5% (v/v), the degree of degradation of the *P. aeruginosa* PAO1 biofilm was 50%, and using a mixture of oil and DNAase I increased it to 72%.

Our studies have shown that in addition to synergistic antimicrobial action, a mixture of *N. vaccinii* IMV B-7405 surfactants with essential oils of cinnamon and lemongrass was effective for the degradation of yeast biofilms. The highest degree (43–60%) of degradation of *C. albicans* D-6, *C. tropicalis* PE-2 and *C. utilis* BMS-65 biofilms was observed by the activity of microbial surfactants and essential oils of cinnamon and lemongrass at a concentration of 300 μg/ml. The use of a mixture of surfactants and EO in a ratio of 1: 1 was accompanied by an increase in the degree of biofilms degradation

Table 8. **Degradation of biofilms of Staphylococcus treated with eugenol, carvacrol, thymol and tetracycline [35]**

Test culture	Concentration (μg/ml) of 50% biofilm degradation						
	Tetracycline	Eugenol	Carvacrol	Thymol	TET* + +1/2 MIC eugenol	TET + +1/2 MIC carvacrol	TET + +1/2 MIC thymol
S. aureus B147	25	630	298	279	11	13	20
S. aureus B285	11	300	247	260	4	8	7
S. mutants B200	36	188	86	143	9	14	24
S. constelatus B629	79	250	98	201	34	51	47

Note: TET — tetracycline; 1/2 MIC — concentration of compound, twice lower than its MIC.

to 70%. In the available literature we found no information about the ability of EO in a mixture with microbial surfactants to increase the degree of destruction of biofilms.

The above results indicate that EO are multifunctional substances that, when used with other compounds (antibiotics, synthetic antifungal agents, surfactants of microbial origin), exhibit synergistic antimicrobial activity and can be effective agents in the fight against biofilms.

Prospects for the practical use of the complex of essential oils with other antimicrobial compounds

Due to their antimicrobial activity, EO are now widely used in medicine (as components of medical preparations), in the food industry (preservation of products), aromatherapy and cosmetology (as parts of body and hair care products, antiseptic oral solutions and toothpastes, perfumes), and agriculture [39–41]. Hereafter we consider the potential uses for complexes of EO with other antimicrobials.

Food industry. The development of pathogenic microbiota on food leads to food poisoning, often with fatal cases. According to the Ministry of Health of Ukraine, the number of food poisonings in the territory of Ukraine amounted to 173 835 cases over the last five years, of which 669 cases were lethal [http://moz.gov.ua/]. Using a complex of EO with antibiotics in the food industry would allow to prevent and stop the development of pathogenic microbiota on products and to minimize the amount of food poisoning.

In [42], the authors established the synergistic antimicrobial activity of essential oil of *Mentha longifolia* and nisin on *Bacillus cereus* and *Bacillus subtilis*, which are among the major food pathogens. A mixture of EO and antibiotics (at concentrations equal to their MIC values) was added to barley broth, in which test cultures were grown for 18 h at 30 °C. The exposure was 15 days at 8 °C and 25 °C. Complete destruction of *B. cereus* and *B. subtilis* cells was observed in the broth at 8 °C on the 15th and at 25 °C on the 12^{th} and 3^{rd} days, respectively.

Bajpai et al. [43] showed that a mixture of *Metasequoia* EO (1–2% v/v) and nisin (0.062–0.5 mg/ml) had an antimicrobial effect on *Listeria monocytogenes* ATCC 19116 in cow milk with varying fat content (1%, 8% and fat free). Irrespective of fat content in milk, complete inhibition of growth of ATCC 19116 strain was observed at a concentration of 1% oil and 0.5 mg/ml nisin after 14 days. Increasing the EO concentration to 2%, allowed to inhibit pathogen's growth in the test culture at a lower (0.062 mg/ml) concentration of nisin in the mixture.

Veterinary medicine. There are severe infectious animal diseases caused by the development of opportunistic microorganisms, which significantly reduce the populations of farm animals [44–47]. The use of a complex of antibiotics with EO makes it possible to prevent and reduce the development of infectious diseases.

Among the most serious problems of farming are the respiratory diseases of cattle, in particular calves, caused by the development of opportunistic bacteria *Mannheimia haemolytica* and *Pasteurella multocida* [44]. When ingested, these bacteria cause lung necrosis and ulcers of the trachea and larynx.

Altough antibiotics doxycycline and tilmicocin are actively used to control *M. haemolytica* and *P. multocida*, over time, their antimicrobial activity is reduced, because of the development of resistance in pathogens. In [44], it was found that MIC of doxycycline and thymicocin decreased by several times when using a mixture of antibiotics with thymol and carvacrol. In most cases FIC did not exceed 0.5, indicating synergism of antimicrobial activity (Table 9).

The pig farms suffer a constant increase in the economic losses through the dying of pigs caused by the epidermitic infections of *Staphylococcus hyicus* and *S. aureus*, resistant to β-lactam antibiotics [45, 46]. The authors of [45] suggest using the essential oils of cinnamon, cumin and thyme as an alternative to antibiotics. It was found that in the presence of 0.078% cinnamon EO (v/v), the degradation of *S. hyicus* 84-2978 biofilm reached 90%, and at the same concentration of cumin EO the degradation of *S. aureus* biofilm ATSC 25923 was 64%.

One of the largest pests of fisheries is the bacteria *Aeromonas* spp. Hence, de Souza et al. [47] investigated the synergistic antimicrobial activity of lemon verbena and bushy lippia EO with florfenicol.

It was found that the MIC of lemon verbena and bushy lippia was 390.6 μg/ml and MIC of florfenicol was 1.95 μg/ml against *Aeromonas* spp. Using a 1: 1 mixture of EO with florfenicol, this ratio was reduced to 97.6 μg/ml for EO and 0.06 μg/ml for antibiotics.

Thus, these few reports indicate the effectiveness of using EO in complex with antibiotic nisin in the food industry and with other antibiotics in veterinary medicine.

Table 9. **Antibacterial activity of mixture of essential oil components with antibiotics against pathogens of infectious respiratory diseases of calves [44]**

EO component	Test culture	MIC of EO component, mM	Antibiotic	MIC of antibiotic, μg/ml	FIC
Carvacrol	*Mannheimia haemolytica*	1.5	Doxycyclin	0.125	0.125
			Tilmicosin	4.0	0.5
	Pasteurella multocida	2.5	Doxycyclin	0.25	0.25
			Tilmicosin	1.0	0.5
Thymol	*Mannheimia haemolytica*	0.625	Doxycyclin	0.125	0.5
			Tilmicosin	4.0	0.75
	Pasteurella multocida	1.25	Doxycyclin	0.25	0.5
			Tilmicosin	1.0	0.5

Thus, in this review it was shown that studies of the synergistic activity of essential oils with other antimicrobial compounds are a relatively new trend that has been actively developing over the last decade. The largest number of publications concerns synergism of antimicrobial activity of essential oils with antibiotics, due to the increasing number of microorganisms, resistant to these preparations. However, essential oils as antimicrobial agents have high minimum inhibitory concentrations and that presents a problem. If, though, essential oils are used in a complex with antibiotics with, there is a decrease in the MIC indices of each of the antimicrobial compounds, and the probability of antibiotic-resistant forms of pathogenic microorganisms is also lower.

In addition to the synergism of antimicrobial activity, a mixture of essential oils with antibiotics or synthetic preparations has a synergistic effect on the destruction of yeast and bacterial biofilms.

At the same time, published information on the synergistic antimicrobial activity of essential oils with microbial surfactants is extremely limited. And there is no data on their synergistic effect on biofilms. Our studies have shown that surfactants of *N. vaccinii* IMV B-7405 have a synergized antimicrobial activity in combination with essential oils of tea tree, cinnamon and lemongrass, reducing the MIC of oils by one to three orders of magnitude. Using surfactant complex of *N. vaccinii* IMV B-7405 with essential oils allowed to degrade the biofilms of yeast of the genus *Candida* by 70%.

It should be noted that a significant advantage of biodegradable and non-toxic microbial surfactants as antimicrobial and anti-adhesive agents is the mechanism of their action, disrupting the integrity of the cytoplasmic membrane, which reduces the possibility of emerging resistant microorganisms.

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СИНЕРГІЧНА ДІЯ НА МІКРООРГАНІЗМИ КОМПЛЕКСУ ЕФІРНИХ ОЛІЙ З ІНШИМИ БІОЦИДАМИ

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В огляді наведено дані літератури і результати власних досліджень стосовно синергізму антимікробної активності ефірних олій з антибіотиками щодо бактерій родини *Enterobacteriaceae*, родів *Staphylococcus*, *Pseudomonas*, *Acinetobacter*, синтетичним антифунгальним препаратом флуконазолом — щодо дріжджів роду *Candida*, поверхнево-активними речовинами мікробного походження — щодо бактеріальних і дріжджових тест-культур, а також про синергічну дію комплексу ефірних олій з антимікробними сполуками (антибіотики, ензими, поверхнево-активні речовини) на біоплівки. Використання суміші ефірних олій з іншими біоцидами дає змогу зменшити у кілька разів мінімальні інгібуючі концентрації кожного з компонентів окремо, а також знизити ймовірність появи резистентних до антибіотиків форм патогенних бактерій і дріжджів завдяки антимікробній дії ефірних олій, що виявляється у порушенні функції плазматичної мембрани мікроорганізмів. Обговорюються перспективи практичного використання комплексу ефірних олій з антибіотиком нізином у харчовій промисловості та іншими антибіотиками — у ветеринарії.

Ключові слова: ефірні олії, антимікробні сполуки, синергізм антимікробної дії, деструкція біоплівок.

СИНЕРГИЧЕСКОЕ ДЕЙСТВИЕ НА МИКРООРГАНИЗМЫ КОМПЛЕКСА ЭФИРНЫХ МАСЕЛ С ДРУГИМИ БИОЦИДАМИ

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В обзоре представлены данные литературы и результаты собственных исследований о синергизме антимикробной активности эфирных масел с антибиотиками по отношению к бактериям семейства *Enterobacteriaceae*, родов *Staphylococcus*, *Pseudomonas*, *Acinetobacter*, синтетическим антифунгальным препаратом флуконазолом — по отношению к дрожжам рода *Candida*, поверхностно-активными веществами микробного происхождения — по отношению к бактериальным и дрожжевым тест-культурам, а также о синергическом действии комплекса эфирных масел с антимикробными соединениями (антибиотики, энзимы, поверхностно-активные вещества) на биопленки. Использование смеси эфирных масел с другими биоцидами позволяет уменьшить в несколько раз минимальные ингибирующие концентрации каждого из компонентов в отдельности, а также снизить вероятность появления резистентных к антибиотикам форм патогенных бактерий и дрожжей благодаря антимикробному действию эфирных масел, состоящему в нарушении функции плазматической мембраны микроорганизмов. Обсуждаются перспективы практического использования комплекса эфирных масел с антибиотиком низином в пищевой промышленности и другими антибиотиками — в ветеринарии.

Ключевые слова: эфирные масла, антимикробные соединения, синергизм антимикробного действия, деструкция биопленок.