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The synthesis of new analogs of natural biologically active substances is a promising direction for the development of effective antifungal agents. Thiosulfonic acid esters (thiosulfonates) are the structural analogs of biocidal compounds from garlic, onion, cabbage, cauliflower, etc. More than 1000 thiosulfonates of various structures of the general formula RSO$_2$SR' were synthesized at the Lviv Polytechnic National University, where their physicochemical properties were characterized. A high antifungal activity of the obtained substances was established in relation to the representatives of fungi of different genera. The thiosulfonates are perspective as basis for the development of effective antifungal means for the modern pharmaceutical, food industry, for the protection of various materials and agricultural products. To increase their effectiveness, antimicrobial compositions based on thiosulfonates and surfactants of microbial origin (biosurfactants) in the form of stable suspensions were developed and studied. It has been established that the use of biosurfactants in the compositions allows the enhancement of the antifungal activity of thiosulfonates and reduction of their active concentration. The possible mechanisms of the joint action of thiosulfonates and biosurfactants on fungal pathogens are proposed.
Esters of thiosulfonic acids are effective sulfenilating reagents in organic synthesis \[19, 20\] and also have valuable properties for solving complex problems of molecular biology and biochemistry \[16\].

Nowadays, synthesis and investigation of thiosulfoesters are carried out by Japanese \[21\], American \[22\], Italian \[23\], Spanish \[17, 24\], Korean \[25\], and Chinese \[26\] scientists from leading research centers. In Ukraine, for many years, the study on the synthesis and physicochemical and biological properties of thiosulfonic acid esters is carried out at the Lviv Polytechnic National University by the staff of the Department of Technology of Biologically Active Compounds, Pharmacy, and Biotechnology \[16, 27\]. At the present time, a scientific school has been formed that develops a methodology for research on the synthesis of biologically active compounds of the thiosulfonate structure.

During this time more than 1000 compounds of the general structure $R\text{SO}_2SR'$ were synthesized:

- $\text{Alk} - \text{SO}_2 - \text{S} - \text{Alk}$
- $\text{Ar} - \text{SO}_2 - \text{S} - \text{Alk}$
- $\text{Cykl} - C_5H_9 - \text{SO}_2 - \text{S} - \text{Alk}$
- $\text{Cykl} - C_6H_{11} - \text{SO}_2 - \text{S} - \text{Alk}$
- $\text{Cykl} - C_5H_9 - \text{SO}_2 - \text{S} - \text{Cykl}$

Among esters of thiosulfoacids, there are compounds with fungicidal activities against fungi of the genera $\text{Candida}$, $\text{Fusarium}$, $\text{Mucor}$, $\text{Phragmidium}$, $\text{Ramularia}$, $\text{Penicillium}$, $\text{Aspergillus}$, $\text{Cladosporium}$, $\text{Paecilomyces}$, $\text{Phoma}$, $\text{Rhizopus}$, $\text{Saccharomyces}$, $\text{Botrytis}$, $\text{Stachybotrys}$, $\text{Alternaria}$, $\text{Aureobasidium}$, $\text{Chaetomium}$, $\text{Myrothecium}$, $\text{Epidermophyton}$, $\text{Trichophyton}$, $\text{Microsporum}$, $\text{Sclerotinia}$, $\text{Monilia}$, $\text{Trichoderma}$, $\text{Verticillium}$, $\text{Pullularia}$, $\text{Cryptococcus}$, $\text{Trichosporon}$, and $\text{Geotrichum}$ \[4–16\].

Investigation of esters of thiosulfonic acids began after the isolation of natural antibiotic allicin from the garlic juice, which manifests the antimicrobial activities. Allicin is a low stable allyl ester of allylthiosulfine acid \[17\]. Esters of thiosulfonic acid, in comparison with esters of thiosulfine acid, are stable compounds; the effectiveness of its antimicrobial activity, in particular, antifungal, is equal to or higher than the activity of thiosulfinates \[17\].

The antimicrobial activity of esters of thiosulfoacids is closely related to their ability to block the normal metabolism of microorganisms through sulfenylation of thiol groups of their enzymes \[28\]. It is known that these esters are highly reactive compounds that interact with nucleophiles, electrophiles, and radicals. Nucleophilic substitution reactions occur with breaking of $-\text{S-S-}$ bond due to the redistribution of electron density in thiosulfogroup that determines the direction of nucleophile attack \[9, 16, 29\].

The information in the review about the possibility of practical application of thiosulfonates as antifungal substances is based on published data on its use in the modern pharmaceutical, food, other industries, and agriculture.

### 2. Protection of agricultural products

Plant-fungal infections cause great economic losses due to the reduction in crop yields during its growing and storage. The loss of crops at all stages of production ranges from 15 to 40%. To solve these problems, esters of thiosulfonic acid can be used.
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used because they are characterized by low toxicity and are permitted as preservatives for the food industry [30–34]. The products of their decomposition are environmentally safe, so these substances do not harm the environment [29, 35].

S-esters of thiosulfonic acid are proposed for the prevention and control of agricultural products damage, in particular, fruit and vegetable, as these compounds are capable of inhibiting or eliminating rotting processes [36].

2.1 Effect of thiosulfoesters on microorganisms

The minimal inhibitory concentrations (MIC) against such fungi (Penicillium sp., Aspergillus sp., Fusarium sp., Rhizopus sp., Mucor sp., Saccharomyces ellipsoideus, Candida albicans) were determined for alkyl, cycloalkyl, trichloromethyl, aryl, and alkyl-functionalized esters of alkane and cycloalkane thiosulfonic acids (Table 1).

| Compound | MIC (μM) |
|----------|----------|
| AlkSO₂SR' |          |

Table 1. Minimal inhibitory concentrations of AlkSO₂SR'.

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It has been shown that the fungicidal activity of cyclopentyl (## 9, 20, 22, 24, Table 1) and cyclohexyl S-esters of alkanthiosulfonic acids (## 10, 21, 23, 25, Table 1) is similar or higher than the activity of alkyl S-esters of alkanthiosulfonic acid (## 1–4, 11–14, Table 1), especially for Fusarium sp., Mucor sp., and Candida albicans.

The minimal inhibitory concentration for cyclopentyl S-esters (## 9, 20, 22, 24, Table 1) varied from 0.5 to 50.0 μg/ml, and for cyclohexyl S-esters, it was in the range of 0.2–5.0 μg/ml. For cyclohexyl S-esters of alkanthiosulfonic acid (## 10, 21, 23, 25, Table 1), the inhibitory concentration is from 0.2 to 2.0 μg/ml relative to Fusarium sp., and Candida albicans [28, 29]. For cyclohexyl S-esters of alkanthiosulfonic acid (## 10, 21, 23, 25, Table 1), the minimal inhibitory concentration ranged from 0.2 to 2.0 μg/ml against Fusarium sp. and Candida albicans [37, 38].

Among the S-esters of cyclopentane-hexanethiosulfonic acid (## 1–19, Table 2) and cyclohexanethiosulfonic acid (## 10–19, Table 2), trichloromethyl S-esters (## 4, 13, Table 2) are most effective against Fusarium sp. and Candida albicans [38] but less active against Mucor sp. [38].

It has been found that cyclopentyl C₆H₅-SO₂-S-C₆H₁₁-cycl (# 6, Table 3) and cyclohexyl C₆H₅-SO₂-S-C₅H₉-cycl (# 3, Table 3) S-esters of benzenthiosulfonic acid C₆H₅-SO₂-S-C₆H₁₁-cycl (# 6, Table 3) exhibit high activity against Candida albicans (MIC 2.0 μg/ml and 1 μg/ml, respectively), Fusarium avenaceum (MIC 5.0 μg/ml and 2.0 μg/ml, respectively), and a lower activity against Mucor sp. [38].

Table 2: Minimal inhibitory concentrations of cycl-AlkSO₂SR' [38].

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2.2 Anti-phytopathogenic activities of esters of thiosulfoacids

The prospects for the use of esters of thiosulfonic acid for the control of clamp rot of beet have revealed. The causative agents of clamp rot of beet are phytopathogens *Botrytis cinerea*, *Fusarium betae*, and *Phoma betae*, which cause the loss of root resource during its storage. These pathogens damage the roots of beet seedlings, cause spotty leaves, and dry rot of root crops, which lead to a decrease in the taste and commodity performance of products. In laboratory conditions, 18 esters of thiosulfoacid were investigated against these phytopathogens (Table 4) [39].
The highest efficacy against *Botrytis cinerea* and *Fusarium betae* was observed for trichloromethyl S-esters of ethane and propanethiosulfonic acid (#7, 11, Table 4). Trichloromethyl S-ester \( \beta \)-naphthalene thiosulfonic acid is less active among the synthesized trichloromethyl esters. The most effective against *Phoma betae* are methyl S-ester of methanethiosulfonic acid (#1, Table 4), ethyl and butyl S-esters of ethanethiosulfonic acid (#5, 6, Table 4), and propyl ester of propanethiosulfonic acid [10]. It has been shown that thiosulfoesters (#1, 7, 11, Table 4) at a concentration of 200 \( \mu \)g/ml are toxic to sugar beet (\*Beta vulgaris var. saccharifera\*) but have fungicidal activity against these phytopathogens. It is interesting that trichloromethyl S-esters of methane- and propanethiosulfonic acids, as well as methyl S-esters of methanesulfonic acid at a concentration of 200.0 \( \mu \)g/ml, are nontoxic to sugar beet but exhibit a fungicidal effect on the abovementioned phytopathogenic fungi.

Approval in the farm conditions of the trichloromethyl S-ester of propanethiosulfonic acid (#11 Table 4), as well as its mixtures with methyl-S-ester of methanesulfonic acid revealed its effectiveness for the treatment of sugar beet root crops for prolonged storage. Improvement of the quality parameters of sugar beet after treatment with the synthesized preparations was established.

Thus, the objects of study were the roots of beet of different qualities. Wilted roots on 15%, damaged ones near the head and tail, roots with 3–4% of green mass and 10% of the earth, and healthy clean roots were used in experiments. After 104 days of storage, all samples of beet treated with solutions of these substances had rotten roots in 2.5–4.0 times less than in untreated control. The effectiveness of the preparations based on the esters of thiosulfonic acid against the causative agents of clamp rot is confirmed by comparative studies of healthy sugar beet with control, where the amount of rotten mass is greater by 9.3 times [39].

The high antifungal activity of alkyl and trichloromethyl esters of methane-, ethane-, and propanethiosulfonic acids in experiments in vitro was discovered. These data indicate that these compounds can be used for the prevention of fruits and vegetables against fungal damage during prolonged storage. Effective fungicidal concentrations of synthesized nine esters of alkanthiosulfonic acid were found for 13 genera of fungi (Table 5): \( C_2H_5SO_2SR \) (#2с, 2е), \( RSO_2SCH_3 \) (#1а, 2а, 3а), \( RSO_2SCl_3 \) (#1b, 2b, 2d, 3b).

The highest fungicidal activity of trichloromethyl esters was found at concentrations of 40–1.25 \( \mu \)g/ml, while alkyl esters of alkanthiosulfonic acids exhibit fungicidal activity at concentrations of 5–100 \( \mu \)g/ml against fungi of the genera *Fusarium*, *Rhizopus*, and *Mucor*, which in some cases is higher than for trichloromethyl esters [40].

The antifungal activity of some alkyl and trichloromethyl esters of aromatic thiosulfonic acids as preservatives for protecting fruits and vegetables during storage against fungal damage was also studied (Table 6) [40].

The positive effect was observed after the use of 4-aminophenyl ester of 4-aminobenzenesulfonic acid (#2a, Table 6) to prevent potato rot during storage. It is significant that this ester is less toxic than alkyl esters of alkanthiosulfonic acid. The potato was treated with a solution of this substance at concentrations of 40 and 20 \( \mu \)g/ml (at a rate of 100 ml or 4–8 mg of dry substance per 1 ton of potatoes). After 1.5 months storage, the amount of potato waste decreased by 2.5 times. The ability of some esters of thiosulfonic acids to protect tomatoes from fungal damage during storage was also studied. The most active and low toxic were the ethyl...
It was established that the treatment of tomatoes by these preparations in laboratory conditions was accompanied by a significant decrease in the amount of waste after 10–12 days of storage.

The effectiveness of alkyl esters of 4-aminobenzenethiosulfonic acids against phytopathogens—the causative agents of citrus fruits' damage—was studied. Citrus fruits were purchased in the Ukrainian trade networks (Lviv). Mycelial fungi *Ramularia chelidonii* and *Phragmidium fragariae* were isolated and identified as pathogens, which cause the damage of lemons and mandarins. It has been shown that isolated cultures exhibit middle and high sensitivity to all studied esters (Table 7). Growth inhibition zones of isolated microorganisms at concentrations of active substances of 0.5% and 1% were on average 25–30 mm [41].

In experiments, the ability of S-ethyl ester of 4-aminobenzenethiosulfonic acid (ETS) to elicit an antifungal effect against pathogens of fruit and vegetable damage was tested. Minimal inhibitory and minimal fungicidal concentrations against four genera of fungi *Aspergillus*, *Penicillium*, *Paecilomyces*, and *Cladosporium* by methods of diffusion and serial dilutions at a microbial load of 5 × 10^5 CFU/ml were determined (Table 8) [41].

2.3 Effect of Propyl propanethiosulfinate and Propyl propanethiosulfonate on phytopathogens

Propyl propanethiosulfinate (PTS), C_3H_7SOS, and propylpropanethiosulfonate (PTSO), C_3H_7SO_2SSC_3H_7, isolated from garlic (*Allium sativum L.*) and onion (*Allium cepa L.*) were proposed by the Spanish researches for the prevention and control of fungal diseases of plants, for crop storage and as disinfectants for food industry, and for the sanitary treatment of cold rooms, equipment, fruit packaging, and vegetables. PTS and PTSO can be used both in pure form and in the form of aqueous mixtures or suspensions with other synthetic or natural antifungal agents, fertilizers, antioxidants, and plant growth regulators. These compounds can be used in different ways such as immersion, wetting, spraying, applying to soil, etc. [17].

The results, presented in Table 9, indicate that PTSO is more active compound against *Penicillium solitum* (wild-type strain) than less stable PTS. These substances are effective protection agents of tomatoes, peppers, cucumbers, melons, lettuce, stone fruits, citrus fruits, strawberries, tropical fruits like avocado, and mango against *Pseudoperonospora cubensis*, *Phytophthora infestans*, *Erysiphe* sp., *Sphaerotheca* sp., *Leveillula taurica*, *Botrytis cinerea Pers.* *Alternaria dauci*, *Alternaria citri*, *Venturia inaequalis*, *Monilia fructicola*, *Monilia laxa*.
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**Taphrina deformans**, **Phytophthora spp.**, **Phytophthora infestans**, **Oidium fragariae**, and **Colletotrichum gloeosporioides** [17], which cause downy mildew, **Botrytis** (gray mold), **alternariosis**, **spotted**, **powdery mildew**, **Monilia**, **bruised**, **Alternaria** of citrus fruits, and **gummosis**.

Pathogens **Penicillium expansum**, **Botrytis cinerea**, **Physalospora obtusa**, **Glomerella cingulata**, and **Botryosphaeria ribis** can cause blue mold, gray mold, black rot, sour rot, and white rot in postharvested apples, pears, and quince [17].

### 3. Protection of materials against biodamage

A serious problem is the biodamage to various materials and products, which is accompanied by annual economic losses. Therefore, there is a need to find ways to solve problems related to the protection of raw materials and products from the action of causative agents during its prolonged storage, transportation, and operation.

In view of this, S-esters of thiosulfonic acid $\text{RSO}_2\text{SR}$ can be promising biocides to protect materials and products since they have a wide range of antifungal and antibacterial effects. The sulfonyl and thiol component of S-esters determines their biocidal action spectrum; therefore, it is important to expand the information on the correlation of the dependence of the structure of S-esters of thiosulfonic acids with its useful characteristics [14, 42].

Ninety-three esters of thiosulfonic acids of various structures in relation to the protection of industrial materials (adhesives, wood, paper, textiles, leather, lubricating liquids, paints, and polymer products) against the fungi, yeasts, bacteria,
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Even at a concentration of 0.15% by weight is noneffective, whereas the effective fungicidal concentration of the ETS is 0.01% by weight (Table 11). The MIC and MFC of the ethyl S-ester of 4-aminobenzenethiosulfonic acid are, respectively, 40–160 and 2–160 times lower than those of the reference preparation. The advantage of the ETC is its solubility in organic hydrocarbon compounds, which provides its effect in the total volume of the organic phase of petroleum products.

In addition, the introduction of the ETC into the emulsion reduces the damage to the equipment of the oil and oil refining industry as a result of increasing the corrosion resistance of materials [44].

Experimental and industrial studies have shown the stabilization of the lubricating liquids by the addition of ETC, which increases the usage period of ones. In the control cycle during cold rolling of the metal, the number of microorganisms in lubricating liquids after 6 days was 60 million/ml, that is, 30 times more than in the experimental cycle after using the ETS (2 million/ml).

The ETC improves the physicochemical parameters of lubricating liquids and reduces emulsion consumption and the time to replace the spent emulsion. As a
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The use of ETC as an antifungal agent for lubricating liquids and emulsion in technological processes creates favorable sanitary and hygienic conditions of work and solves a number of environmental issues [44].

4. The effect of ethylthiosulfanilate on the fungal infections

According to the WHO, more than 20% of the world's population of different age groups is affected by mycoses, especially mycoses of the feet and hands with the damage to the nail plate. The resistance of fungal pathogens to known drugs causes increased mycosis diseases and their complications (secondary infections, allergic reactions, eczema, etc.).

It is well known that ETS exhibits a broad spectrum of antifungal activity against pathogenic fungi [4, 5, 14]. The antifungal effects of ETS against 17 strains of various fungi were studied. It has been found that the MIC of the ETC varies from 3.6 to 500 μg/ml (Table 12) and depends on the genus and strain [5, 52].

The causative agents that cause skin and systemic diseases are yeast of the genus Candida. The antifungal activity of ETS was determined for the most virulent representatives of Candida albicans, Candida tropicalis, and Candida stellatoidea. The MIC of ETS for C. albicans is 30 μg/ml, C. tropicalis 250 μg/ml, and for C. stellatoidea 500 μg/ml. ETS is highly effective against Aspergillus foetidus and Acremonium chrysogenum, MIC of which is 3.6 μg/ml and 62.5 μg/ml, respectively (Table 12) [5, 52, 53]. ETC was proposed as an active substance of the antifungal 1% Esulanum ointment after a detailed study of the antimicrobial effects of a number of esters of thiosulfonic acids in S. Ordzhonikidze All-Union Scientific-Research Institute.
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This ointment was developed based on doegling oil and intended for the treatment of tinea pedis and other fungal skin diseases [4, 5, 54].

The advantage of the Esulanum ointment is its keratolytic properties, which promotes rapid penetration of the drug in the deep tissue and provides an effective long-term therapeutic effect [5, 54].

The study of antimicrobial activity of 1% Esulanum emulsion ointment in vitro against a number of microorganisms (Staphylococcus aureus, Streptococcus haemolyticus, Escherichia coli, Salmonella typhosa, Flexner's Bacillus dysenteriae, Diphtheria bacillus (strain PW3), Bacillus pyocyaneus, Proteus vulgaris, Anthrax spores, Human tubercle bacillus (H37), Avian tubercle bacillus, Mycobacterium B5, Microsporum lanosum, Trichophyton gypseum, Achorion schoenleinii, Actinomycetes, and fungi Candida albicans, Aspergillus niger) showed fungicidal properties of the active substance of the ETS. In this case, the MIC and MFC of ETS are practically similar [5].

Clinical studies of the therapeutic effect of 1% ETS ointment in patients with various forms of fungal skin diseases (epidermophytosis, rubrophytosis, microsporia, and trichophytosis) and different clinical manifestations have proven their effectiveness. Based on these results, an instruction for the application of 1% ETC ointment (Esulanum) was developed by the Pharmacological Committee of the Ministry of Health of the former USSR [5].

Experimental part production of 1% Esulanum was introduced into medical practice, but taking into account that the basis of the dosage form was doegling oil, which resources were limited, industrial production was not realized.

The study of the qualitative and quantitative composition of the dosage form based on the ETS and its therapeutic effects is ongoing. The dynamics of the death of C. tropicalis cells affected by fungicidal concentrations of the ETS on the model system, similar to human organism processes (37°C), using a microorganism suspension with a cell load of 4 × 10^5 cells/ml, were detected. It has been found that the minimum fungicidal concentration for cells is 250 μg/ml [52]. Thus, the fungicidal effect of the ETS on C. tropicalis is founded after 30 min of exposure (9.09%) and after an hour by 98.48%, and the full therapeutic effect is achieved after 6 h of exposure.

Adding ETS in fungicidal concentrations to the growth medium changes the morphogenesis of C. tropicalis. Bumps and fractures appear on the surface of yeast cells, and their manifestation depends on the time of exposure [52]. ETC affects the metabolism of C. tropicalis, suppressing endogenous respiration by 87% and the decrease in nucleic acid pool in pathogen cells to 27.52% for DNA and up to 39.13% for RNA. Significant differences were observed in C. tropicalis lipogenesis under the influence of this biocide. Thus, subfungicidal concentration of ETS reduces the concentration of almost all classes of phospholipids in cells but increases in the content of lysophosphatidylcholine by 16.25% and phosphatidylcholine by 11.11% [52].

The ETC at fungistatic and subfungicidal concentrations exhibits a membranotropic effect and provides a high degree of cooperability of the membrane structural transitions of cells [55, 56]. The functional state of cell membranes of C. tropicalis was assessed by the release of low molecular nucleotide component from cells (pyrimidine and purine bases) under the action of various concentrations of the ETS. Detection of substances at λ = 260 nm is a sensitive test that characterizes the state of the barrier permeability of the membrane and can be used to study the kinetics of this process.

The obtained results showed that the release of low molecular nucleotide components from C. tropicalis begins immediately after the adding of ETS into the medium (C. tropicalis cells concentration, 10^6 cells/ml). The increase of output of purine and pyrimidine-containing compounds from the cell in 4.8 times compared...
to reference cells was observed, changing the concentration of ETS from 0 to 62.5 μg/ml. The concentration of ETS in the range of 62.5–125 μg/ml causes almost complete loss of these compounds' pool.

The increase in the permeability of *C. tropicalis* membranes under the influence of different concentrations of the ETS or different time of its exposure can be related to high saturation of cell membranes by lipids. The change in permeability of membranes under the action of ETC is probably due to their dynamic structure. Interaction of ETS and the surface structures of the cell initiate deep structural rearrangements of membranes, which results in increased permeability and, possibly, inhibition of one's physiological functions.

The obtained data suggest that the mechanism of action of the ETS may be related to the disruption of the cytoplasmic membrane, which will lead to significant defects in the delivery of nutrient components to cells and the removal of vital metabolites from them.

So, summing up our results, it can be considered that the mechanism of ETS effects can be related to the disruption of the cytoplasmic membrane that leads to significant defects in the flow of nutrients into the cells and the removal of metabolites from ones [55].

5. Compositions of esters of thiosulfoacids and biosurfactants and their effects on microorganisms

Alkyl esters of alkane- and arene-thiosulfonic acids are hydrophobic compounds, since they are poorly soluble in water, which limits their use as antimicrobial agents. In addition, the surfaces of microbial cells provide the protective barrier to antimicrobials. To increase the solubility and bioavailability of the thiosulfonates, substances that are capable of their solubilization are used, in particular, surface-active substances (surfactants), which can be used as components of ointments, gels, and creams. The most promising ones are biogenic surfactants—products of microbial synthesis (biosurfactants) [57, 58]. Vasileva-Tonkova et al. [59] and Sotirova (2012) described the permeabilizing effect of biosurfactants. They can interact with membrane phospholipids, influence cell hydrophobicity, and have emulsifying ability [53, 59].

The formation of the supramolecular complexes of rhamnolipids with model membrane phospholipids is considered as a possible molecular mechanism of membranothropic action of the biosurfactant, which was shown by electrospray ionization mass spectrometry [60]. These complexes can affect the liquid-crystalline state of the lipid matrix of microbial membranes and change some membrane processes such as cells transport [61].

The permeabilization of cell membranes with surfactants can overcome the barriers and increase the efficacy of various antimicrobial agents. In this regard, biosurfactants can play a significant role as additives in the development of pharmaceuticals due to their ability to enhance solubility or bioavailability of poorly soluble substances [58].

A new promising approach to the creation of effective antimicrobials is proposed, which consists in a synergistic combination of thiosulfonic esters, ethylthiosulfonilate (ETS) or methylthiosulfonilate (MTS), with the biosurfactants of *Pseudomonas* sp. PS-17 strain—rhamnolipid biocomplex (RBC) and rhamnolipids (RL). The introduction of biosurfactants into the compositions allowed the reduction of the active concentrations of thiosulfonates in the resulting products. The antimicrobial potential of compositions based on ETS and MTS with RL was investigated against model strains of various genera and taxonomic groups.
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capable of causing damages to human health, agriculture, industrial products, as well as phytopathogens. So, for culture Rhizopus nigricans, MFCs for MTS, 30 μg/ml, and for ETS, 50 μg/ml, and for their compositions RL were, respectively, 10 and 20 μg/ml [53, 60].

The explanation of these results could be related to permeabilization of the microbial cell membranes by rhamnolipids (increase in levels of extracellular proteins). Biosurfactants provoke changes in cell surface and affect different components of the membranes [62]. Biosurfactant also can damage the surface structure of the spores [53, 63].

The developed ointment composition exhibits high antifungal and antibacterial activity in comparison with known biocidal agents. The addition of rhamnolipid biosurfactants into thiosulfonate compositions contributed to the decrease of minimal fungicidal and bactericidal concentrations [53, 64]. The criteria for selecting the ratios of ETS and RBC in the compositions were the formation of stable emulsions and the antifungal and antibacterial activity of the compositions.

Comparative studies of the effectiveness of ointment preparations based on ETC and the composition of ETS + RBC with respect to microorganisms of various taxonomic groups were carried out (Table 13). Thus, the presence of the biosurfactant enhanced the biocidal effect of MTS and ETS. A possible explanation could be related to the higher protein leakage as a result of permeabilization with the rhamnolipid biosurfactant. Probably, the decrease in concentrations of the studied substances, which are able to suppress the microbial growth completely, is due to the increased access of inhibitors to the bacterial cell.

The use of rhamnolipids or other biosurfactants active against variety of microorganisms, in combination with antibiotic treatment, or antimicrobials, may represent new productive antimicrobial strategy [65].

6. Antifungal activity of various esters of carboxylic and heterocyclic thiosulfonic acids

The series of alkyl-, cycloalkyl- and aryl-esters of arylthiosulfonic acids RNHC₆H₄SO₂SR’ was synthesized, and the spectrum of their antifungal action was studied (Table 14) [27].

For RNHC₆H₄SO₂SR’ (Table 14), MIC was determined for Candida albicans ATCC 90028, Candida glabrata ATCC 90030, Aspergillus fumigatus IHEM 13934, and MFC for Candida albicans, Verticillium dahliae, Trichophyton gypseum. All synthesized esters are characterized by rather high fungicidal activity. The compounds...
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with an acetyl fragment exhibit a higher fungicidal activity than compounds with a 3-chloropropionyl or trifluoroacetyl fragments. The MIC of ethyl ester of 4-acetylaminobenzenethiosulfonic acid relative to *C. albicans* is 25 μg/ml and for fungi *A. fumigatus*, 12.5 μg/ml, while the MIC of the ethyl ester of 4-trifluoroacetyl aminobenzenethiosulfonic acid was, respectively, 50 and 25 μg/ml. Regarding the influence of substituents (R') from the side of sulfide sulfur, cycloalkyl- and aryl thiosulfone esters were more active than alkylic. The MFC values of phenyl esters of 4-acetyl and 3-chloropropionyl aminobenzenethiosulfonic acids were determined between 2–10 and 10–40 μg/ml, respectively.

The evaluation of the fungistatic effect of methyl, ethyl, and allyl esters of 3-acetylamino-4-methoxybenzenethiosulfonic on test-cultures of *C. albicans* and *Penicillium* sp. with an exposure time of 24–120 h was conducted [64]. At a concentration of 200 μg/ml methyl and allyl esters partially delay growth at exposure for 24 h. With an exposure of 48 h at a concentration of 100 μg/ml, allyl ester completely inhibits the growth of *C. albicans*, which is associated with a change in the antifungal mechanism [66].

People with reduced immunity are often exposed to disease, provoked by fungal infections. It was established that alkyl esters of alkane and arylthiosulfonic acids, alkyl esters of heterocyclic thiosulfonic acids have high antifungal activity. MIC of alkyl esters of 2,3-dioxo-1,2,3,4-tetrahydroquinoxaline-6-thiosulfonic acid was established for various fungal strains of *Candida*, *Cryptococcus*, *Trichosporon*, and *Geotrichum* [67–71]. For fungi of the genus *Candida*, the most effective is the allyl ester (**C₃H₅**) (**Table 15**).
This regularity is characteristic to fungi of genera Cryptococcus, Trichosporon, and Geotrichum (Table 16).

The fungistatic effect of methyl, ethyl, and allyl esters of 8-quinolinethiosulfonic acid on the test-culture of C. albicans exposed during 24–120 h was evaluated. For all...
investigated esters, the inhibitory concentration is 200 μg/ml. Ethyl and allyl esters are more active and their MIC is 100 μg/ml. At a concentration of 1.0 μg/ml, the ethyl ester partially delay the growth of the test-culture exposed for 24–48 h [70, 71].

Summing up our results of the antimicrobial activity of esters of thiosulfonic acids, various ways of their practical application can be proposed. It has been shown that there is a correlation between the structure of thiosulfonate esters, their reactivity in chemical and biochemical reactions, and biological activity. This is confirmed by the specificity of the effects of thiosulfonates against various pathogenic fungi, depending on the structure of their sulfenyl and thiol components. Our finding showed the advantages of synthetic esters of thiosulfonic acids in comparison with their natural analogs by the biological activity, as well as their competitiveness compared with commercial antifungal substances. The competitiveness of thiosulfonates is determined by their low fungicidal and bactericidal concentrations and low resistance of microorganisms to their action. Thus, new thiosulfoacid esters as biologically active compounds are suitable for the development of more efficient and safe medicines, biocides, remedies, and growth stimulators.
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