PRIMARY MICROBIOLOGICAL SCREENING OF AMINO ACIDS AND THEIR MODIFIED VARIANTS

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The primary microbiological screening of 20 native amino acids and 52 modified variants thereof was carried out. A significant antimicrobial activity was established for synthetic derivatives against reference strains of gram-positive microorganisms (*S. aureus* ATCC 25923, *B. subtilis* ATCC6633), mild antimicrobial activity of new compounds towards gram-negative microorganisms (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853) and weak antimicrobial activity against *Candida* spp. fungi (*C. albicans* ATCC 885-653). The results of the primary microbiological screening of modified amino acids prove the relevance and potential of the further thorough study of the range and level of antimicrobial activity of the certain selected compounds with the aim to develop new antimicrobial agents.

Keywords: modified amino acids, microorganisms, antimicrobial activity

The Fight against infectious diseases is still the most relevant problem in medicine [1]. Antimicrobial chemical agents have the leading role in prophylaxis and treatment of diseases of microbial genesis [2]. The main negative consequence of antibiotic therapy is the progressive resistance of the microorganisms [3-5]. Therefore it is necessary to introduce rational application of the existing antimicrobial agents; to develop and carry out research programs aimed at overturning the resistance; to search for new, highly effective medicinal and prophylactic agents that differ in their influence on microorganisms, especially on multi-resistant strains [6]. The search among the natural and synthetic biologically active compounds that influence the development of resistance in against antibacterial agents in the clinically relevant strains acquires increasingly greater significance [7]. With increasing frequency, the specialists turn to the natural treatment approaches, especially towards plants that possess antibacterial activity and towards the compounds that compose the biological structure of the organisms and display various properties.

The aim of the study – to substantiate microbiologically the use of new antimicrobial agents based on the modified amino acids variants.

Materials and methods

20 native amino acids and 52 synthetic derivatives of 7 amino acids were studied, All synthetic compounds were produced and characterized at the department of pharmakognosia (manager Koshoviy O. M.) of the national pharmaceutical university of the Health Ministry of Ukraine. The analyzed amino acids were classified into 7 research groups based on their chemical composition and were assigned their own codes. 9 amino acids with aliphatic radicals were studied, including leucine derivatives 3.1 - 3.3, isoleucine derivatives 4.1 - 4.3, glycine derivatives 5.1, 5.2, and 5.3. Also 43 amino acids derivatives that contained an additional functional group in their aliphatic radical: carboxyl - aspartic acid derivatives, 1.1 - 1.3; amide – asparagine derivatives 2.2 - 2.5; amino group – lysine derivatives 6.1, 6.1.1 - 6.1.7; 6.2, 6.3 - 6.7; guanidine group – arginine derivatives 7.1, 7.1.1 – 7.1.11, 7.2–7.11.

For the primary screening standard test cultures of gram-positive and gram-negative bacteria were used that belonged to different taxonomic groups: *Staphylococcus aureus* ATCC 25923, *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *Bacillus subtilis* ATCC6633*, Proteus vulgaris ATCC 4636*. Antifungal activity of the compounds was studied for the reference strain of *Candida albicans* ATCC 885-653.

Determination of antimicrobial and anticandidal activity of the new compounds was carried out with the help of the standard methods of double serial dilution in the nutritive medium (macromethod). The testing was carried out in the volume of 1 ml of each dilution of the compounds with the final concentration of the studied microorganism approximately 5×10^5 CFU/ml. After incubation in course of 24 or 48-72 hours for the *Candida spp.* cultures, the probes with the cultures were studied with the help of light microscopy for the microorganisms' growth determination. The minimal inhibiting concentration (MIC) was established according to the minimal concentration of the studied substance that suppressed the visible growth of the culture. For determination of the minimal bactericidal concentration (MBcC) measured seedings onto solid mediums (Muller-Hinton agar) from all the probes where no microorganism growth was observed were undertaken. The lowest concentration that caused death of no less than 99,9% bacteria was accepted as MBcC. During the carrying out of the experiments, the control of culture growth without the studies compounds was undertaken, as well as the growth in the solvent; the control of the purity of the microorganism suspension (through seeding onto non-selective mediums) and the medium sterility.

Results and discussion

Primary screening studies of the antimicrobial activity of the 20 basic amino acids were carried out. Among all studies amino acids, the mild antimicrobial activity against the tested reference strains of gram-positive and gram-negative microorganisms was observed only for two amino acids – lysine and glycine. In course of the screening against gram-positive test strains (*S. aureus* ATCC 25923 та *B. subtilis* ATCC 6633) it was established that the inhibiting activity of lysine and glysine was observed at concentrations 15,6 –

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31,2 μg/ml. MBcC of the above mentioned amino acids against *S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633 was 31,2 μg/ml. As a result of experiments with the gram-negative test strains of microorganisms (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853), it was established that only lysine and glycine exhibited mild bactericidal and bacteriostatic activity (MIC and MBcC in the range 31, 25 – 62,5 μr/ml). Antifungal activity against test strain of *C. albicans* ATCC 885-653 was not observed in any studied amino acid.

Based on the results of the experiments, the sensitivity level of test strains of gram-positive microorganisms (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633), to the synthetic derivatives of aspartic acids, asparagine, leucine and isoleucine, unlike the corresponding native amino acids (Fig. 1) was found to be significantly high. MIC of all above mentioned amino acids was in the range of 7,8 – 31,25 μg/ml, and no studies derivatives of asparagine, isoleucine and leucine had MIC above 15,6 μg/ml against *S. aureus* ATCC 25923. The bactericidal activity of the new synthetic derivatives of aspartic acid, asparagines, isoleucine, leucine and glycine against test strains of gram-positive microorganisms was mainly mild (MBcC in the range of 15,6 – 62,5 μg/ml compared to the MBcC of the native amino acids 250,0 μg/ml).

New derivatives of aspartic acid, asparagine, leucine and isoleucine have not exhibited noticeable anti fungal properties. MIC and MBcC of the representatives of these groups of new compounds – synthetic derivatives against test strain of *C. albicans* ATCC 885-653 was in the range 62,5 – 250,0 μg/ml and 125,0 – 500,0 μg/ml respectively (Fig. 1).

All synthetic derivatives of glycine have exhibited high activity against gram-positive test strains (Fig. 2). MIC of all the compounds of this group against *S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633 was in the range of 7,8 – 15,6 μg/ml (compared to the MIC of the native glycine 31,25 μg/ml). As for the activity against reference test strain of *C. albicans* ATCC 885-653 new derivatives of glycine, as well as compounds from all previous groups have not exhibited considerable activity (MIC in the range of 125,0– 250,0 μg/ml, MBcC – 250,0 – 500,0 μg/ml compared to the MIC and MBcC of native glycine 500,0 μg/ml).

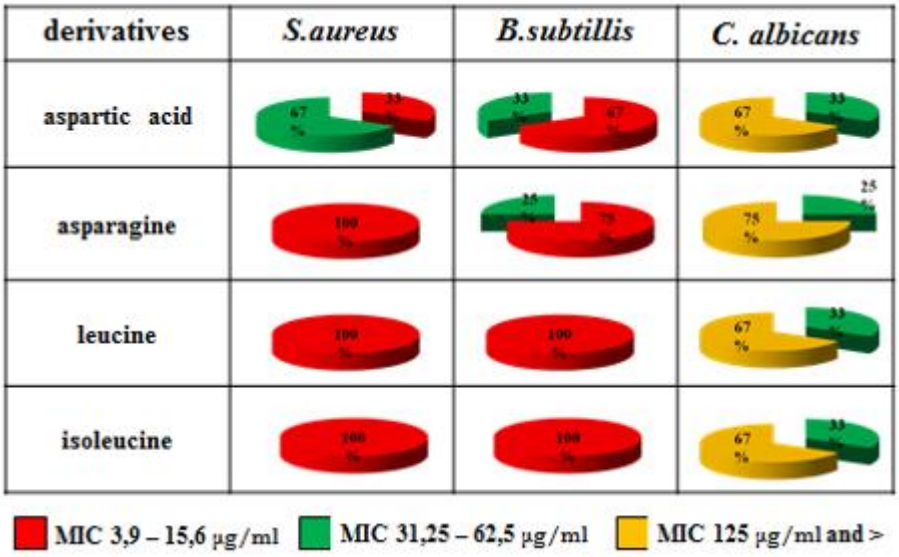

Fig. 1. Results of the primary microbiological screening of the synthetic derivatives of asparagines, aspartic acids, leucine and isoleucine against gram-positive microorganisms and *Candida* spp, fungi

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In course of the screening of the 14 synthetic derivatives of lysine against the *S. aureus ATCC 25923* test strain, it was established that the inhibiting activity of all compounds of this group was in the concentrations 3,9 – 15,6 μg/ml, which corresponded or was higher than the value for the native amino acid (MIC of lysine 15,6 μg/ml) (Fig. 2). The number of lysine derivatives – compounds 6.1, 6.1.1 and 6.1.2 (21,4 % of studied samples), have exhibited inhibiting activity, more pronounced compared to the native lysine (MIC of the compounds 3,9 μg/ml). It was experimentally proven that MBcC of all the compounds of the given group (92,9 %) was in the range 7,8 – 15,6 μg/ml, which was somewhat higher than the values for the native amino acid (MBcC of lysine 31,25 μg/ml).

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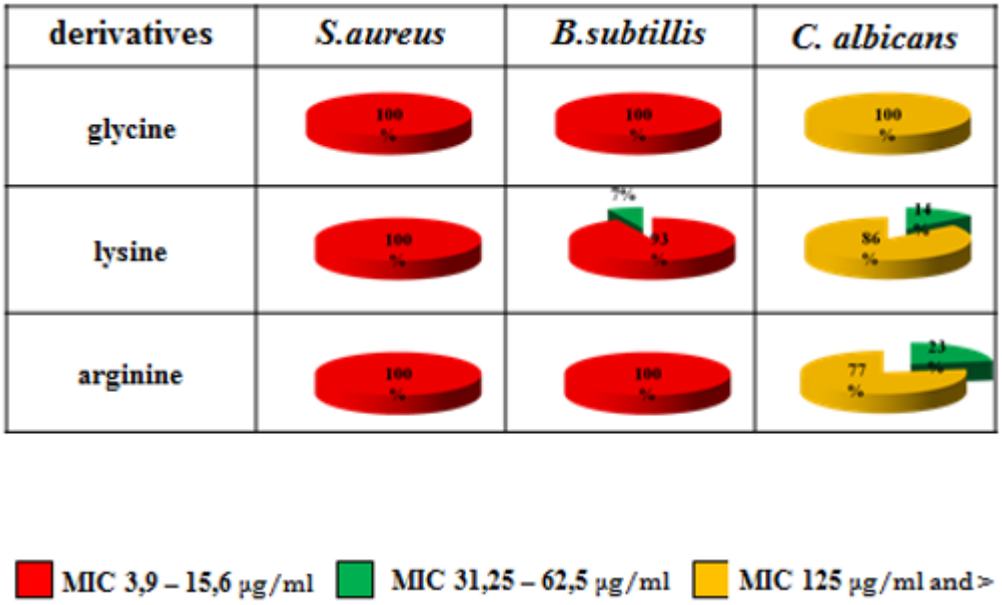

Fig. 2. Results of the primary microbiological screening of the synthetic derivatives of glycine, lysine, and arginine against gram-positive microorganisms and *Candida* spp. fungi

The sensitivity of the test strain *B. subtilis* ATCC 6633 to the synthetic lysine derivatives was almost similar. 93 % synthetic lysine derivatives exhibited relatively high bacteriostatic activity (MIC in the range 3,9 – 15,6 μg/ml), higher than the native amino acid (MIC of lysine was 31,25 μg/ml). The majority of the lysine synthetic derivatives (85,7 %) exhibited high bactericidal activity against this strain with the MBcC in the range of 7,8 – 15,6 μg/ml, that was also higher than the native amino acid (MBcC of lysine 31,25 μg/ml). Therefore, among 14 lysine synthetic derivatives the most active compounds exhibited the highest activity against reference strains of gram-positive microorganisms (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633) were compounds 6.1, 6.1.1 and 6.1.2 (MIC 3,9 μg/ml and MBcC 7,8 MIC in the range), and their antimicrobial properties were higher compared to the other compounds of this group, as well as native lysine.

According to the experimental results, only 14,3 % of the studies new lysine derivatives have exhibited mild antifungal activity against test strain *C. albicans* ATCC 885-653 (MIC 62,5 μg/ml) (Fig. 2). The strain *C. albicans* ATCC 885-653 was the most sensitive only to the two agents - 6.1 та 6.5. In general, the sensitivity of *C. albicans* ATCC 885-653 test strain to the overwhelming majority of the new lysine synthetic derivatives was weak.

In course of the screening of the 22 arginine synthetic derivatives, it was established that all compounds exhibited high activity against *S. aureus* ATCC 25923 test strain (Fig. 2). MIC of the above mentioned test strains was in the range 3,9– 15.6 μg/ml and MBcC in the range of 7,8 – 31.25 μg/ml, that was several times higher than the native amino acid value (MIC and MBcC of arginine was 125,0 and 250,0 μg/ml, respectively). Inhibiting activity of almost the third of the arginine synthetic derivatives (27,3 %) was observed at concentration of 3,9 μg/ml, which was significantly higher than the values for the other compounds of this group, as well as the native amino acid value (MIC of arginine 125,0 μg/ml). Inhibiting activity against *S. aureus* ATCC 25923 with MIC 3,9 μg/ml was exhibited by the compounds: 7.1.3, 7.1.5, 7.1.6, 7.1.7, 7.1.11. The same arginine derivatives exhibited the highest bactericidal activity (MBcC 7,8 μg/ml).

The sensitivity of the *B. subtilis* ATCC 6633 test strain to the arginine synthetic derivatives was almost as high. 9,1 % of the tested arginine derivatives, namely compounds 7.1.6 and 7.1.7, exhibited bacteriostatic activity (MIC 3,9 μg/ml), significantly higher than the native amino acid (MIC of arginine 125,0 μg/ml). MIC of the rest of the compounds in this group was in the range of 7.8 – 15.6 μg/ml. More than a half of the studied arginine synthetic derivatives (59,1 %) exhibited high bactericidal activity against this test strain with the MBcC in the range 7,8 – 15,6 μg/ml, that was significantly higher than the native amino acid (MBcC 250,0 μg/ml). As for the rest, *B. subtilis* ATCC 6633 was mildly sensitive to the 40,9 % of arginine synthetic derivatives (MBcC 31,25 μg/ml).

Therefore, among the 22 new arginine synthetic derivatives the compounds 7.1.3, 7.1.5, 7.1.6, 7.1.7 та 7.1.11 were the most active against reference strains of gram-positive microorganisms (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633) (MIC and MBcC were in the range 3,9 – 15,6 and 7,8 – 31,25 μg/ml, respectively), and their antimicrobial properties were better than native arginine.

The level of sensitivity of *C. albicans* ATCC 885-653 test strain to the arginine synthetic derivatives was not high (Fig. 2). MIC and the MBcC of the overwhelming majority of this group were in 125,0 – 250,0 μg/ml range. Only 2,7 % of the new arginine derivatives exhibited mild inhibitory activity against the *C. albicans* ATCC 885-653 test strain (MIC 62,5 μg/ml).

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Primary screening studies of the antimicrobial activity of the new compounds against gram-negative microorganisms (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) were carried out. As the result of the study it was established that the reference strains of gram-negative microorganisms (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) were significantly less sensitive to the synthetic derivatives of asparagine, aspartic acid, leucine and isoleucine compared to the gram-positive microorganisms strains (Fig. 3). As for the studies gram-negative strains of microorganisms, the above mentioned new compounds exhibited mostly mild inhibitory activity (MIC 31,25 – 62,5 μg/ml compared to the MIC of the native amino acids in the range of 250,0 – 500,0 μg/ml). Bactericidal activity of the compounds against the test strains if gram-negative microorganisms was also mostly mild or low (MBcC in the range of 62,5 – 125,0 μg/ml compared to the MBcC of native amino acids in the range of 250,0 – 500,0 μg/ml). The synthetic derivatives of isoleucine were the most active among the above mentioned groups. MIC was in the range 3,9 – 15.6 of μg/ml in 67 % isoleucine derivatives against *P. vulgaris* ATCC 4636 and in 33 % against *E. coli* ATCC 25922.

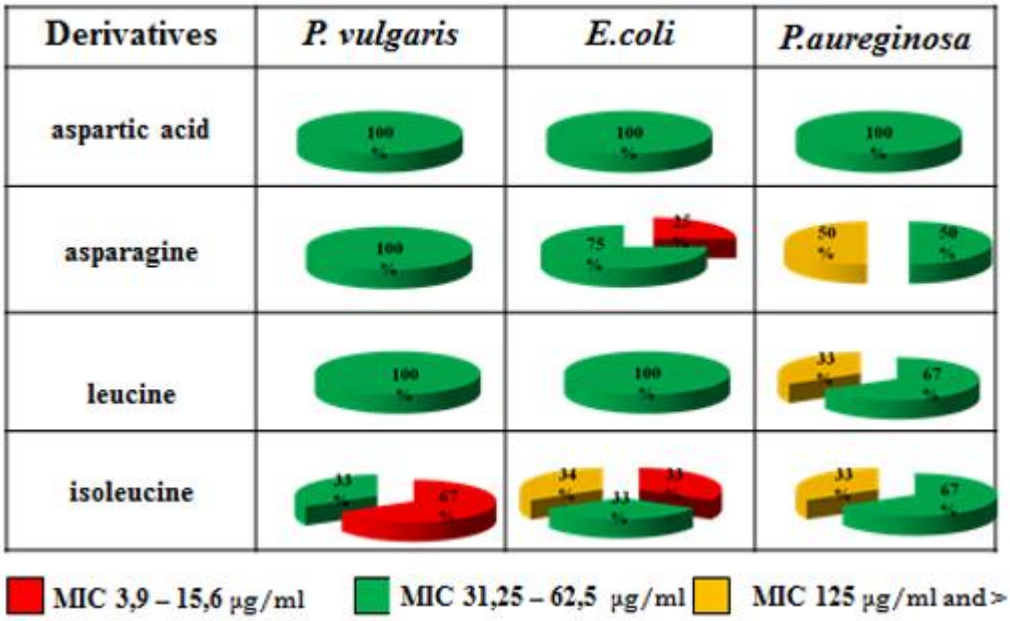

Fig. 3. Results of the primary microbiological screening of the synthetic derivatives of asparagines, aspartic acid, leucine and isoleucine against gram-negative microorganisms

Glycine derivatives, namely compounds 5.1 and 5.2 also exhibited mild inhibitory activity against gram-negative (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) (Fig. 4). MIC of the mentioned above compounds against gram-negative microorganisms were in the range of 31,25 – 62,5 μg/ml and corresponded to the MIC of the native glycine.

As a result of the experiments it was established that 43 % lysine derivatives, namely compounds: 6.1.5, 6.1.6, 6.1.7, 6.2, 6.3 and 6.6, exhibited high bacteriostatic activity against the test strain of *E. coli* ATCC 25922 (MIC in the range 7,8 – 15,6 μg/ml), somewhat higher compared to the native lysine level (MIC 31,25 μg/ml) (Fig.4). Bactericidal activity of the 78,6 % of lysine synthetic derivatives against *E. coli* ATCC 25922 was mainly mild (MBcC 31,25 – 62,5 μg/ml). The most active compound against *E. coli* ATCC 25922 test strain was the compound 6.3 (MIC and MBcC 7.8 μg/ml and 15,6 μg/ml, respectively). Almost 86 % of the new lysine derivatives exhibited mild bacteriostatic activity against *P. vulgaris* ATCC 4636 test strain (MIC 31,25 – 62,5 μg/ml), corresponding or somewhat lower than the native lysine value (MIC 31,25 μg/ml). But mild bactericidal activity (MBcC 62,5 μg/ml), corresponding to the native amino acid level against *P. vulgaris* ATCC 4636 was shown only for the third of this group compounds (28,6 %). The sensitivity of the *P. aeruginosa* ATCC 27853 test strain to the synthetic lysine derivatives was the same. Among all researched synthetic lysine derivatives the compound 6.6 was shown to be the most active against *P. aeruginosa* test strain (MIC and MBcC was 15.6 μg/ml and 31,25 μg/ml, respectively). 79 % of the lysine synthetic derivatives exhibited mild bacteriostatic activity against *P. aeruginosa* ATCC 27853 test strain (MIC 31,25 – 62,5 μg/ml), equal or somewhat lower than the native lysine value (MIC 31,25 μg/ml). But mild bactericidal activity against *P. aeruginosa* ATCC 27853 (MBcC 62,5 μg/ml), equal to the native amino acid level, was shown only for the 21,4 % compounds of this group.

Therefore, among the 14 new lysine synthetic derivatives against reference strains of gram-negative microorganism (*P. vulgaris* ATCC 4636 , *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853), compounds 6.3 and 6.6 were found to be most active.

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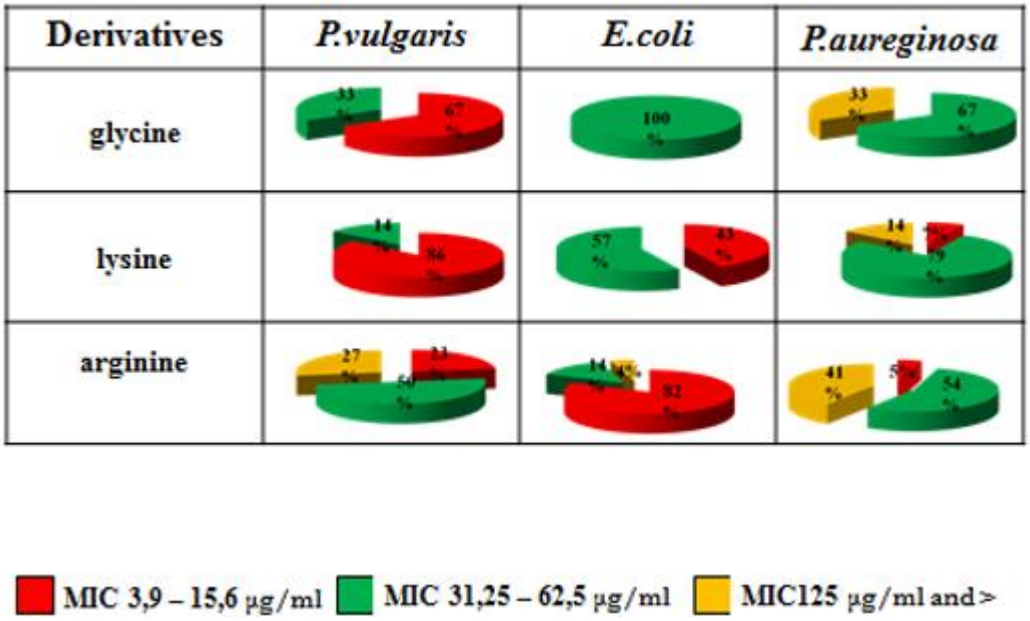

Fig. 4. Results of the primary microbiological screening of the lysine, glycine and arginine against gram-negative microorganisms

The overwhelming majority of the arginine synthetic derivatives (81,8 %) exhibited high bacteriostatic activity against *E. coli* ATCC 25922 (MIC in the range 7,8 – 15,6 μg/ml), significantly higher than the native amino acid value (MIC of arginine 250,0 μg/ml) (Fig. 4). The high bactericidal activity against this reference strain was exhibited by 13,6 % compounds at the concentration of 15,6 μg/ml. Bactericidal activity of the above mentioned compounds was several times higher than the native arginine value (MBcC 250,0 μg/ml). The most active compounds against *E. coli* ATCC 25922 test strains were compounds 7.1.5, 7.1.6, and 7.1.11 (MIC and MBcC 7,8 μg/ml and 15,6 μg/ml, respectively). 77,3 % of the researched new arginine derivatives exhibited mild bactericidal activity against this test strain (MBcC 31,25 – 62,5 μg/ml), significantly higher than the native arginine value.

The activity of the newly synthesized arginine derivatives against the other gram-negative test strains was somewhat lower (Fig. 4). Against *P. vulgaris* ATCC 4636 test strain, 23% compounds exhibited high bacteriostatic activity (M MIC 15,6 μg/ml). High bacterial activity against *P. vulgaris* ATCC 4636 standard strain, significantly higher than the native arginine value (MIC 250,0 μg/ml), was established in compounds 7.1.7, 7.1.10, 7.1.11, 7.7, and 7.8. Mild bacteriostatic activity against *P. vulgaris* ATCC 4636 test strain was noted in the half of the studied arginine derivatives (MIC in the range 31,25 – 62,5 μg/ml). In 45,5% of the studied arginine derivatives, mild bactericidal activity against *P. vulgaris* ATCC 4636 was found in 11,6 % compounds (MBcC 31,25 – 62,5 μg/ml).

The standard strain *P. aeruginosa* ATCC 27853 sensitivity against new synthetic arginine derivatives was almost similar (Fig. 4). High bacteriostatic activity against this strain was found only in the compound 7.1.6 (MIC 15,6 μg/ml). Half of the studied compounds in this group (54,4 %) exhibited mild bacteriostatic activity against *P. aeruginosa* ATCC 27853 test strain (MIC 31,25 – 62,5 μg/ml). 45,5 % of the studied arginine derivatives exhibited mild bactericidal activity against this test strain (MBcC 31,25 – 62,5 μg/ml).

Therefore among the 22 new synthetic derivatives of the amino acid arginine the most active compounds against reference strains of gram-negative microorganisms were (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853) were compounds 7.1.5 and 7.1.6.

Therefore, the primary microbiological screening of the 52 new synthetic amino acid derivatives has shown significant antimicrobial activity of the synthetic compounds against reference strains of gram-positive microorganisms (*S.aureus* ATCC 25923, *B. subtilis* ATCC 6633), mild antimicrobial activity of the overwhelming majority against gram-negative microorganisms (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853), and weak antifungal activity against *Candida* spp, fungi (*C. albicans* ATCC 885-653). For the more detailed study of the range and levels of the antimicrobial activity in the future, the lysine derivative compounds 6.1, 6.1.1, 6.1.2, 6.3, 6.6 and arginine derivative compounds 7.1.3, 7.1.5, 7.1.6, 7.1.7, and 7.1.11 were chosen, in order to develop antimicrobial agents based thereof.

Conclusions

1. Among the studied 20 native amino acids, only lysine and glycine had mild antimicrobial activity against reference strains of gram-negative and gram-positive microorganisms.
2. Primary microbiological screening of the 52 new synthetic amino acid derivatives has shown their high antimicrobial activity against reference strains of gram-positive microorganisms (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633) in 94 % studied compounds (MIC in the range 3,9 – 15,6 μg/ml).

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2. More than 80 % studied synthetic amino acid derivatives have shown high or mild activity (MIC in the range of 7,8 – 62,5 μg/ml) against gram-negative microorganisms test strains.
3. Based on the results of the study, the level of sensitivity of *C. albicans* ATCC 885-653 test strain to the synthetic amino acid derivatives was low.
4. It was proven experimentally that further studies of the range and level of antimicrobial activity of the certain most active compounds with the aim of new antimicrobial and antifungal agents development is both expedient and promising.

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Introduction. The Fight against infectious diseases is still the most relevant problem in medicine [1]. Antimicrobial chemical agents have the leading role in prophylaxis and treatment of diseases of microbial genesis [2]. The main negative consequence of antibiotic therapy is the progressive resistance of the microorganisms [3-5]. With increasing frequency, the specialists turn to the natural treatment approaches, especially towards plants that possess antibacterial activity and towards the compounds that compose the biological structure of the organisms and display various properties. **The aim of the study** – to substantiate microbiologically the use of new antimicrobial agents based on the modified amino acids variants. **Materials and methods.** 20 native amino acids and 52 synthetic derivatives of 7 amino acids were studied, All synthetic compounds were produced and characterized at the department of pharmakognosia of the national pharmaceutical university of the Health Ministry of Ukraine. For the primary screening standard test cultures of gram-positive and gram-negative bacteria were used that belonged to different taxonomic groups. Determination of antimicrobial and anticandidal activity of the new compounds was carried out with the help of the standard methods of double serial dilution in the nutritive medium (macromethod). The testing was carried out in the volume of 1 ml of each dilution of the compounds with the final concentration of the studied microorganism approximately 5×10^5 CFU/ml. The minimal inhibiting concentration (MIC) was established according to the minimal concentration of the studied substance that suppressed the visible growth of the culture. For determination of the minimal bactericidal concentration (MBcC) measured seedings onto solid mediums (Muller-Hinton agar) from all the probes where no microorganism growth was observed were undertaken. The lowest concentration that caused death of no less than 99,9% bacteria was accepted as MBcC. **Results and discussion.** Therefore, the primary microbiological screening of the 52 new synthetic amino acid derivatives has shown significant antimicrobial activity of the synthetic compounds against reference strains of gram-positive microorganisms (*S.aureus* ATCC 25923, *B. subtilis* ATCC 6633), mild antimicrobial activity of the overwhelming majority against gram-negative microorganisms (*P. vulgaris* ATCC 4636, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853), and weak antifungal activity against *Candida* spp, fungi (*C. albicans* ATCC 885-653). For the more detailed study of the range and levels of the antimicrobial activity in the future, the lysine derivative compounds 6.1, 6.1.1, 6.1.2, 6.3, 6.6 and arginine derivative compounds 7.1.3, 7.1.5, 7.1.6, 7.1.7, and 7.1.11 were chosen, in order to develop antimicrobial agents based thereof. **Conclusions.** 1. Among the studied 20 native amino acids, only lysine and glycine had mild antimicrobial activity against reference strains of gram-negative and gram-positive microorganisms. 2. Primary microbiological screening of the 52 new synthetic amino acid derivatives has shown their high antimicrobial activity against reference strains of gram-positive microorganisms (*S. aureus* ATCC 25923 and *B. subtilis* ATCC 6633) in 94 % studied compounds (MIC in the range 3,9 – 15,6 μg/ml). 3. More than 80 % studied synthetic amino acid derivatives have shown high or mild activity (MIC in the range of 7,8 – 62,5 μg/ml) against gram-negative microorganisms test strains. 4. Based on the results of the study, the level of sensitivity of *C. albicans* ATCC 885-653 test strain to the synthetic amino acid derivatives was low. 5. It was proven experimentally that further studies of the range and level of antimicrobial activity of the certain most active compounds with the aim of new antimicrobial and antifungal agents development is both expedient and promising.

Keywords: modified amino acids, microorganisms, antimicrobial activity

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