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SOIL XANTHOMONAS, STENOTROPHOMONAS AND PSEUDOMONAS MULTI-DRUG RESISTANCE AND FIGHTING AGAINST THEM BY NEW DERIVATIVES OF TARTARIC ACID

Bella G. Babayan
National Polytechnic University of Armenia (NPUA),
Basic Research Laboratory of Agrarian Pesticides
Creation and The Quality Control,
105 Teryan St., Yerevan, RA
«Armbiotechnology» SPC, NAS RA Laboratory of
Ecological Safety,
14 Gyurjyan, Yerevan, RA
bbg.15.04@mail.ru
ORCID iD: 0000-0002-3978-1209
Republic of Armenia

Abstract

Antibiotic-resistance of Pseudomonas, Xanthomonas, Stenotrophomonas native soil strains were studied in current paper. The prevalence of their multi-drug resistant representatives was detected. For some strains the causes of plasmid-mediated resistance stability were disclosed. The presence of antibiotic modification *blaOXA-10, catB7, aac(6')II, aph(3')IV* genes (containing in Pseudomonas clinical strains) was detected on both plasmids and nucleoid of observed native bacteria. According to the results of research, tartaric acid (TA) new synthetic derivatives are effective against the multi-drug animal and human opportunistic pathogenic and phytopathogenic representatives of the studied bacteria. Cyclohexyl- substituted imide and complex salts of TA have demonstrated the maximal effect against all the majority of tested pathogens. Complex salts of TA are able to biodegradation by soil non-pathogenic *P. chlororaphis* group bacteria. According to preliminary screening data, their potential eco-toxicological safety was shown.

Key words: tartaric acid derivatives, Pseudomonas, Stenotrophomonas, Xanthomonas, multi-drug resistance.

Introduction

One of the important problems of modern agriculture and healthcare is the struggle against the antimicrobial-resistant pathogens. Antibiotics since the moment of their discovery remains the predominant antimicrobial agents. Thus they are broadly used in various scopes of human activity [1]. But the excessive usage of them fatally decrease the quality of food, agricultural production and finally is being transferred into healthcare problem [2]. The chronic usage of agricultural production which is overvalued by antibiotics led to formation of resistance increase in opportunistic pathogenic and pathogenic micro flora what potentially decreases the efficiency of infections antibiotic therapy. Besides, antibiotics have the range of various disadvantages, such as like the versatile side effects, up to acute and chronic disorders occurrence in patients [3].

Pseudomonas, Xanthomonas and *Stenotrophomonas* are very common microorganisms with a huge potential of adaptivity, which includes the high level of antimicrobial resistance too [4]. They are well-known as xenobiotic-resistant bacteria, which are able to biodegradation of various substances, such as like antibiotics, artificial toxic organic compounds like oil products, etc. being widespread on all the geographical zones of Earth planet, the mentioned bacteria are involved in various consumptions chains as reducers (decomposers) [5,6]. And due to their active participation to intra specific gene horizontal transfer, they can led to uncontrolled spread of antimicrobial resistance genes. The initial source of these genes are native bacteria of soil and water. For the representatives of these three genera the multiple mechanisms of antibiotic-resistance (chemical modification by enzymes, target modification, efflux systems, etc.) are well-known. Moreover, their genes and operons, which are responsible for antibiotic-resistance can be easily mutated by the pressing of antibiotics in case of clinical selection [7,8]. As a result, it might become a cause of a particular strain resistance diapason enlargement (such as like in case of mutant β-lactamases, which are not sensitive to clavulanic acid classical inhibitor. It might led to the formation of new strains of pathogens too. The most dangerous representatives of multi-drug resistant infections are different species of *Pseudomonas* and *Stenotrophomonas* which are opportunistic pathogens of agricultural animals (*P. aeruginosa, S. maltophilia,* etc.). The harm from the phytopathogenic species (*P. syringae, X. beticola, X. vesicatoria,* etc.) of the *Xanthomonas* and *Pseudomonas* is significant for crops too. And due to their high level of adaption the complex and combined agents of animal and plants production are often not so effective [9,10].

Thus, the search of novel classes of chemical compounds against the multiple resistant microorganisms is very actual. One of the direction in these research is the derivativeness of natural antimicrobial compounds, such as like organic acids [11,12]. That is why in NPUA, cyclic imides and complex amine salts of tartaric acid (TA) with improved antibacterial properties were synthesized and tested on more than 200 native strains of animal and human opportunistic pathogenic as well as phytopathogenic and non-pathogenic representatives *Xanthomonas, Pseudomonas, Stenotrophomonas*.

Conflict setting and set of Methodology

All the experiments were carried out with the support of the specialists of RA NAS SPC "Armbiotechnology" on strains form The National Collection of Microorganisms of Microbial Depository Center (MDC). Field tests were carried out with support of Institute of Fish Industry of the National Academy of Sciences of Belarus, the Scientific Center of Agrobiotechnology SNCO, Armenian National Agrarian University [13]. There were used the following strains of bacteria: *P. aeruginosa, P. putida, P. putida, var. melanogenes, P. geniculate, P. chlororaphis (P. chlororaphis subsp. chlororaphis, P. chlororaphis subsp. aurantiaca, P. chlororaphis subsp. aureofaciens), P. taetrolens, P. syringae (P. syringae, pv. syringae, P. syringae pv. lachrymans, P. syringae, pv. tabaci), Pseudomonas sp., P. fluorescens, S. maltophilia, X. campestris, X. vesicatoria, X. beticola*. On these bacteria different concentrations were tested (25mcg/mL, 50mcg/mL, 500mcg/mL) of 13 antibiotics of various classes and generations: penicillin/Pcn, ampicillin/Amp, amoxicillin/Amx, augmentin/Amc, cefixime/Cfx, ceftriaxone/Cro, azithromycin/Azm, ciprofloxacin/Cip, tetracycline/Tcn, chloramphenicol/Cam, streptomycin/Stp, gentamycin/Gnc, kanamycin/Kan. As a control there were used the following sensitive *E. coli DH5α* and antibiotic resistant

strains: *E. coli DH5α*/VOG16, *E. coli DH5α* /pUC18, *E. coli DH5α* /PEC7 [14,15]. Genetic analyses were carried out by plasmid and total DNA isolation by alkaline extraction and benzyl chloride usage. Isolated DNA was studied by 0.8-2.5% agarose gel electrophoresis with application of UV detection by ethidium bromide and bromophenol blue dyes. Plasmid analyses were carried out by electrophoresis and transformation due to Mandel's method of chemically competent cells obtaining by low temperature centrifugation with presence of Calcium chloride. Antibiotic resistance genetic analyses were carried out by PCR analyses of antibiotic modification genes. Lipase and polyphenol oxidase (PPO) activities were identified on solid cultural media due to standard protocols, and measured by the appropriate zones of reaction product accumulation [16-18].

The development of new and comparably safe antimicrobial agents is extremely significant. During the recent decades, antimicrobial properties have been studied for various organic acids: tartaric, lactic, citric, oxalic acids, etc. These substances are now successfully used in world practice for the production of environmentally friendly agrochemicals. TA is especially widely used, being the most common organic acid of plants. This compound, as well as its salts of alkali and alkaline earth metals, are considered safe food additives (E334 - E337, E354). Also, it is used both in free form and in amide forms [19]. That is why, in current paper the effect of a TA synthetic derivatives on more than 200 strains of 6 subspecies of 12 species of soil native *Pseudomonas, Xanthomonas, Stenotrophomonas* is considered. These substances were elaborated in Basic Research Laboratory of Agrarian Pesticides Creation & The Quality Control at National Polytechnic University of Armenia (NPUA) on the basis of natural tartaric acid obtained by purifying it from tartar, according to the technology proposed in our laboratory [20]. The antimicrobial effect and biodegradation potential were tested for Benzylimide of TA, Cyclohexylimide of TA, Phenylimide of TA, cyclohexyl complex amino salt of TA, benzyl amino complex salt of TA, phenyl amino complex salt of TA, ethamonlamino complex salt of TA (EACS). Microbiological evaluation of antibacterial activity and biodegradation potential of TA new derivatives were detected on different solid and liquid cultural media: 1% and 0.7% nutrient agar, L-broth, selective media with antibiotics, M9 mineral salt media with substituted carbon source due to standard protocols [21]. The ability of TA derivatives resistance spread was tested by the methods of transformation and PCR [22]. *In silicon* experiments were carried by the molecular docking with appropriate models of key role proteins of infection and pathogenicity of *Pseudomonas, E. coli* and other Gram-negative opportunistic pathogens. It was carried out due to the methodology, which was elaborated in Russian-Armenian University (RAU), the laboratory of structural bioinformatics and chair of General and Pharmaceutical Chemistry [23]. The statistical evaluation and verification of experiments were carried out due to standard protocols [24].

Research Results

The results of cultivations series of more than 200 strains of *Pseudomonas, Xanthomonas* and *Stenotrophomonas* on various selective media have demonstrated the prevalence of antibiotic-resistance strains, and especially pun-drug and multi-drug strains.

The wide spectrum of diversity of resistance to 13 studied antibiotics from β-lactam, aminoglycoside, fluoroquinolone, azalide macrolide, tetracycline and amphenicole classes was identified for animal and human opportunistic pathogenic, phytopathogenic and non-pathogenic representatives of different species (tab. 1). In strains *P. chlororaphis subsp.*

chlororaphis 9171, Pseudomonas sp.9317 the presence of efflux system was identified. It is responsible for the resistance to gentamycin and kanamycin correspondently. In *Pseudomonas sp. 9269* the same type of resistance is identified to azithromycin, in *Pseudomonas sp. 9267* – to penicillin and ampicillin, in *Pseudomonas sp. 9312, 9333* – to tetracycline, in *Pseudomonas sp. 9325* - to ceftriaxone.

The results of genetic research of the studied both antibiotic-resistant and sensitive strains have demonstrated the diversity of plasmid content in them (Fig. 1). According to the obtained results, some non-plasmid strains were identified among the both resistant and sensitive representatives of different species. Experiments with transformations series have shown the presence in cells of *P. aeruginosa* and *S. maltophilia* various plasmids, which carry more than one genes of antibiotic resistance (*S. maltophilia 306d2*). In some representatives (*P. aeruginosa 9059*) the presence of more than one plasmid with different resistance genes was identified. For all the studied strains of *P. taetrolens* the presence of plasmids was shown which are not responsible for the resistance to 13 studied antibiotics. For *P. taetrolens* there were no detected non-plasmid representatives. For the identification of resistance mechanisms PCR analyses were carried out (Fig. 1-2).

Table 1

Antibiotic-resistance diapason of more than 200 soil native strains of *Pseudomonas, Stenotrophomonas and Xanthomonas* of different species. R - resistant, S – sensitive

Native soil bacteria	Antibiotic-resistance					
	β-lactam	aminoglycoside	Fluoroquinolone	azalide	amphenicole	tetracycline
P. aeruginosa	80%	60%	30%	50%	70%	40%
P. putida	98%	2%	2%	7%	40%	25%
P. fluorescens	99%	10%	22%	32%	24%	30%
P. geniculate	67%	37%	12%	5%	30%	25%
P. taetrolens	60%	12%	35%	35%	57%	35%
P. chlororaphis	79%	18%	21%	6%	31%	20%
P. syringae	98%	62%	57%	63%	50%	58%
Pseudomonas sp.	60%	38%	14%	9%	38%	30%
S. maltophilia	93%	17%	22%	15%	57%	26%
X. vesicatoria	70%	10%	3%	6%	7%	5%
X. beticola	3%	0%	0%	0%	0%	0%

According to PCR analyses, the genes *blaOXA-10, aac(6')II, aph(3')IV, catB7*, which are responsible for antibiotic modification and the resistance to β-lactams, aminoglycosides and amphenicoles were identified in a minority of representatives of *S. maltophilia, P. aeruginosa, P. fluorescens*, etc. Transformation have demonstrated nucleoid localization of resistance streptomycin and chloramphenicol resistance genes in all the representatives of *Stenotrophomonas, Xanthomonas, Pseudomonas*, including *catB7* gene. In some strains mutant forms of genes were identified with blocked or decreased activity (in *P. fluorescens 9087* mutant *blaOXA-10* gene with decreased enzyme activity, in *P. chlororaphis, subsp. chlororaphis 9171* – mutant *aac(6')II* gene with decreased activity and in *P. putida 9249* mutant inactive *aac(6')II* gene), while in other ones there were detected mutations which led to increase of resistance, such as like in case of augmentin-resistance (in *P. putida 9249, P. fluorescens 9110, P. fluorescens 9070* mutant *blaOXA-10*, with resistance to clavulanic acid). For all the studied plasmids of *Pseudomonas, Xanthomonas, Stenotrophomonas* different species the stabile replication in non-selective conditions was identified.

For the identification of cases of stability, the series of analyses of other enzymes of these plasmids were carried out which potentially may be involved in xenobiotic biodegradation and cause the stability. There were studied extracellular lipase polysorbate degradation and L-tyrosine, tannin and α-naphtol degradation by PPO. Due to the obtained data, the maximal extracellular activity of lipases and PPO were detected for *P. chlororaphis* group (Fig. 3).

Also, the same was registered for *P. aeruginosa*, *P. putida* and *S. maltophilia* representatives. In various species of *S. maltophilia*, *P. chlororaphis* 3 subspecies, *P. taetrolens*, the presence of lipases was detected which were able to degradation of polysorbates with different length of fatty acid residue (Polysorbate -20, -40, -60, -65, -80, -85).

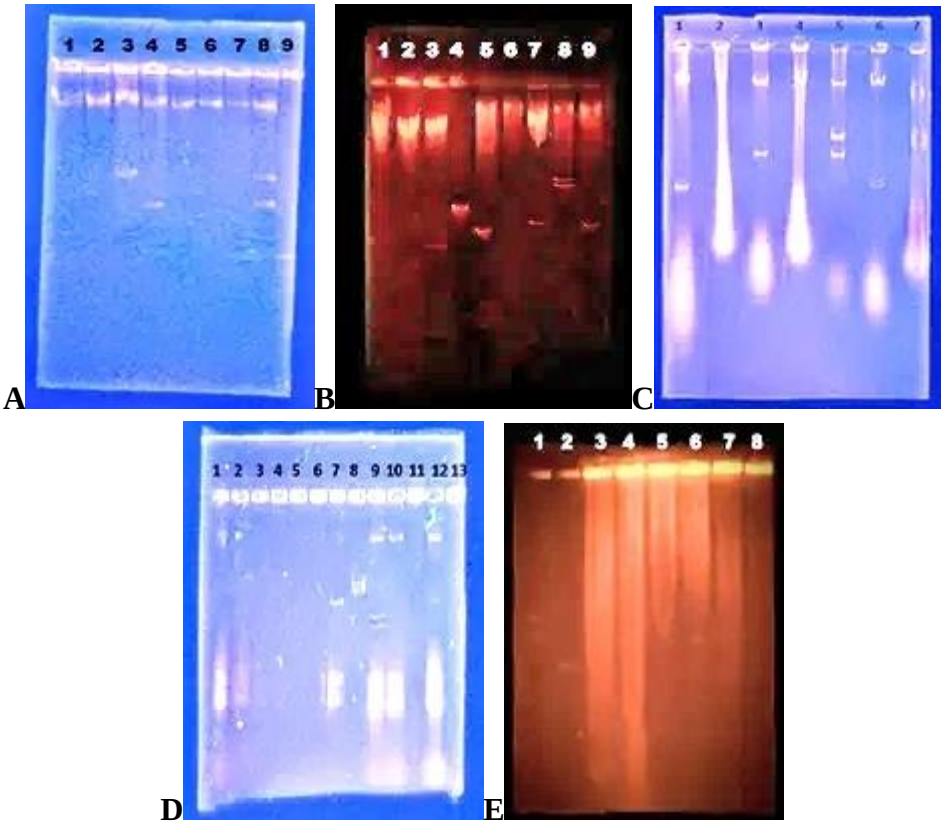

Fig. 1 DNA electrophoresis of different strains

A: 1 – P. putida 9234, 2 – P. putida 9238, 3 - P. putida var. melanogenes 9254, 4 – P. putida var. melanogenes 9253, 5 – P. putida 9227, 6 – P. putida 9223, 7 – P. putida var. melanogenes 9252, 8 – P. putida 9230, 9 – P. putida 9249; B: 1 – P. geniculate 9341, 2 – P. geniculate 9336, 3 – P. geniculate 9337, 4 – P. geniculate 9211, 5 – P. geniculate 9202, 6 – P. geniculate 9203, 7 – P. geniculate 9209, 8 – P. geniculate 9212, 9 – P. geniculate 9205; C: 1 – P. taetrolens 9240, 2 – P. taetrolens 9242, 3 – P. taetrolens 9243, 4 – P. taetrolens 9244, 5 – P. taetrolens 9248, 6 – P. taetrolens 9246, 7 – P. taetrolens 9241. D: 1 – S. maltophilia 9303 , 2 – S. maltophilia 9308, 3 – S. maltophilia 9286 , 4 – S. maltophilia 9290 , 5 – S. maltophilia 9293 , 6 – S. maltophilia 9273 , 7 – S. maltophilia 306d2, 8 – S. maltophilia 9285, 9 – S. maltophilia 9289, 10 – S. maltophilia 9306 , 11 – S. maltophilia 9297, 12 – S. maltophilia 9300, 13 – S. maltophilia 9307; E: 1 – P. syringae path. lachrymans 8732, 2 – X. vesicatoria 8647, 3 – P. syringae, path. syringae 8736, 4 – X. beticola 8680, 5 – P. syringae, path. tabaci 8663, 6 – P. syringae, path. tabaci 8665, 7 – S. maltophilia 9286, 8 – X. beticola 8681.

The differences in substrate specificity profiles of enzymes was detected. For some strains of *S. maltophilia* there were identified enzymes, which were able to degradation of only one type of polysorbates, while in other strains lipases were destructing all the studied polysorbates or few of them (such as like for P. chlororaphis 3 subspecies).

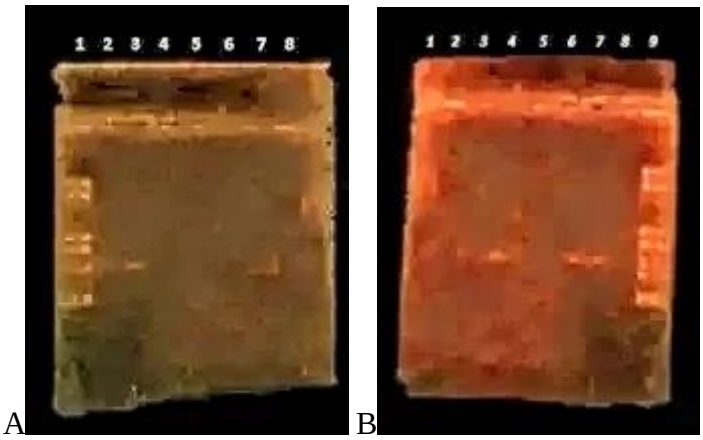

Fig. 2 A: PCR analysis of *catB7* in *P. aeruginosa*

1 – control (EcoRI/Hind III), 2 – *P. aeruginosa 9059*, 3 – *P. aeruginosa 5249a*, 4 – *P. aeruginosa 5249b*, 5 – *P. aeruginosa* 9057, 6 – *P. aeruginosa 9058*, 7 – *P. aeruginosa 9056*, 8 – *P. aeruginosa 9057*; B - PCR analysis of *blaOXA-10* in *P. putida* and *P. geniculate*. 1 – *P. geniculate 9335, 2 – P. geniculate 9202, 3 – P. geniculate 9340,* 4 – *P. putida 9230, 5* - 6 – *P. putida 9234*, 7 – *P. putida 9249*, 8 – *P. putida 9216*, 9 – control.

The transformation analyses have demonstrated the diversity of localization of their genes both on plasmids and nucleoid. Also, the presence of plasmid-localized and nucleoid genes of lipases with different substrate specificity was demonstrated for *P. taetrolens* and *S. maltophilia*.

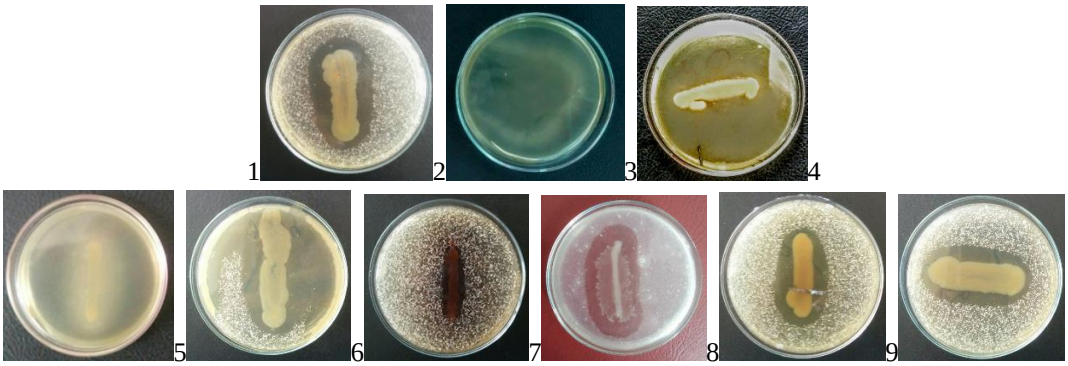

Fig. 3 *Pseudomonas* and *Stenotrophomonas* extracellular lipases precipitation by fatty acids Ca salts accumulation on solid mineral M9 media with substitutes by polysorbates carbon source

1 – P. chlororaphis subsp. aurantiaca 9061 on polysorbate-20, 2 – P. taetrolens 9246 on polysorbate-85; 3 – S. maltophilia 9302 on polysorbate-85; 4 – S. maltophilia 9288 on polysorbate-85; 5 – P. putida 9229 on polysorbate-60; 6 – P. fluorescens 9072 on polysorbate-40; 7 - P. chlororaphis, subsp. chlororaphis 9168 on polysorbate-20; 8 – P. putida var. melanogenes 9254 on polysorbate-20; 9 – Pseudomonas sp. 9257 on polysorbate-20.

PPO were also identified in different species representatives of *Pseudomonas*, *Stenotrophomonas* and *Xanthomonas.* This property is correlating with tetracycline-resistance in a majority of cases. The maximal level of activity was observed for *P. chlororaphis* group representatives. Due to genetic analyses by transformation method, in all the studied microorganisms, the genes of these enzymes were encoded by nucleoid (Fig. 4).

Then the series transformations of sensitive strains by the plasmids, which were isolated from the strains, which have demonstrated lipase and PPO activity. As a result, it was found out that in S. maltophilia, some resistance plasmids stability is related to the presence on them lipases genes.

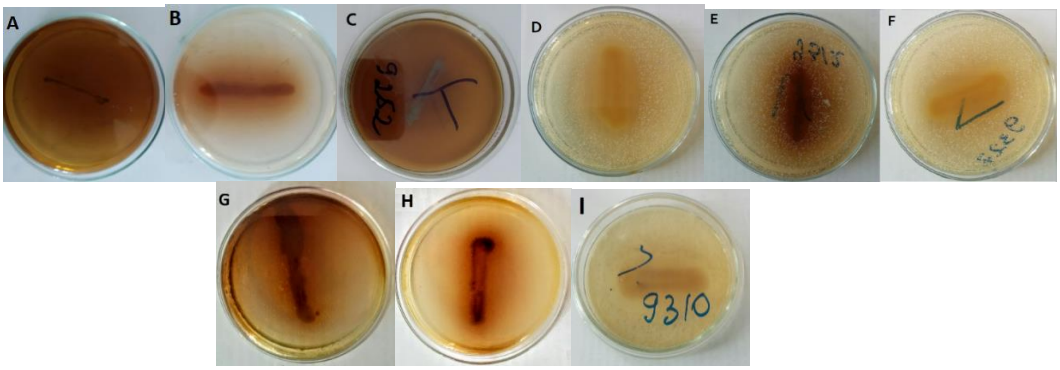

Fig. 4 *Pseudomonas and Stenotrophomonas* polyphenol oxidases (PPO) precipitation by the accumulation of tannin, α-naphtol, L-tyrosine degradation in mineral M9 media with carbon source which was substituted to PPO substrates.

A – α-naphtol biodegradation by PPO II (lakase) of P. fluorescens 9075; B – (PPO I) tyrosinase of P. geniculate 9335; C – tannin biodegradation by PPO II, PPO III of P. putida, var. melanogenes 9252; D – tyrosinase of P. geniculata 9336; E – tyrosinase of Pseudomonas sp. 9312; F – tyrosinase of Pseudomonas sp. 9327; G – tyrosinase of S. maltophilia 9288; H – tyrosinase of S. maltophilia 9302; I – tyrosinase of S. maltophilia 9310.

For P. taetrolens it was shown the ability of their plasmids to transmit the lipases genes. For some of them it was identified more than one lipase genes on plasmids and nucleoid with different substrate specificity [25, 26].

At the next step of current research, on all the studied bacteria there were tested 7 new synthetic derivatives of TA. As a result, emphasized bactericidal effect of cyclohexylimide and cyclohexyl amino complex salt of TA was detected. Benzyl- and phenyl substituted imides and complex amino salts were effective too, but the strains in which PPO were active, were predominantly resistant to these compounds.

This property was shown for non-pathogenic *P. chlororaphis* group different species representatives, as well as for *P. fluorescens*. By the transformation series, it was demonstrated impossibility of that properties transmission to other Gram-negative bacteria by plasmids.

The negative results were obtained for *P. aeruginosa 9056*, as well as *E. coli, S. maltophilia, X. beticola, P. carotovorum* and other bacteria. Some resistant to TA derivatives P. chlororaphis have demonstrated the ability of growth on mineral media containing cyclohexyl-, phenyl-, benzyl- complex amino salts, by utilizing it as carbon source. Imides didn't demonstrate that properties. Cyclohexyl-, benzyl- and phenyl- derivatives have demonstrated their efficiency against the opportunistic pathogenic strains of *P. aeruginosa, P. putida, P. geniculate, S. maltophilia*, as well as against the phytopathogenic bacteria of *X. vesicatoria, X. Beticola, P. syringae* [27].

For the study of mechanism of antimicrobial activity of TA derivatives, the series of in silico experiments were carried out. According to molecular docking analysis, the binding of TA cyclic and ethanolamine synthetic derivatives to some membrane proteins and transcription factors was found out which are responsible for the pathogenicity of bacteria and infection of host organism: TsaR (3FXQ) transcription regulator of *P. testosteroni*, BenM, benzoate receptor quorum sensing regulator of *P. aeruginosa*; OXYR (1I69) hydrogen peroxide sensor of y *E. coli*. The binding take place predominantly by the hydrophobic aminoacids residues, with the formation of hydrogen, van der Waals, hydrophobic bonds. Cyclohexyl- and benzyl- derivatives have demonstrated the maximal binding to the studied model proteins.

Conclusions

Among above than 200 studied *Pseudomonas, Stenotrophomonas* and *Xanthomonas* soil strains of animal and human opportunistic pathogens, phytopathogens and non-pathogenic decomposers species the wide diversity of resistance was detected. Multi-drug resistant representatives of them are resistant to the antibiotics of last generations (such as like azithromycin and ceftriaxone). In genome of the studied strains different genes of resistance were identified, including efflux systems and antibiotic modification genes *blaOXA-10, aac(6')II, catB7, aph(3')IV* both on bacterial chromosome and plasmids. Genes of chloramphenicol streptomycin resistance are related only with nucleoid. The plasmids diversity was identified in both sensitive and resistant strains. The plasmids which are not related with 13 studied antibiotics were identified too. In *P. taetrolens*, no plasmids of resistance to these 13 antibiotics were identified. Biodegradation extracellular lipases and PPO were identified in resistant and sensitive strains. In one part of them lipases genes are related to stability of antibiotic resistance plasmids. PPO genes are identified only in nucleoid of all the studied strains. TA synthetic derivatives in forms of imides and complex amino salts are effective against both phytopathogenic and opportunistic pathogenic representatives of *Pseudomonas, Stenotrophomonas* and *Xanthomonas,* as bactericide agents. Cyclohexyl derivatives have demonstrated the maximal activity. All the tested salt forms are biodegradable by soil non-pathogenic *P. chlororaphis* group representatives. The resistance to them is not transmitted by plasmids and might be relate to nucleoid localization of PPO genes. Thus, further research becomes interesting with the prospective antibacterial agents against the multi-drug resistant pathogens of animals and plants with possible application in agriculture, horticulture and veterinary.

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ՀՈՂԱՅԻՆ XANTHOMONAS, STENOTROPHOMONAS, PSEUDOMONAS ԲԱԶՄԱԿԱՅՈՒՆՈՒԹՅՈՒՆԸ ԵՎ ԴՐԱ ԴԵՄ ՊԱՅՔԱՐԸ ԳԻՆԵԹԹՎԻ ՆՈՐ ԱԾԱՆՑՅԱԼՆԵՐԻ ՄԻՋՈՑՈՎ

Բ.Գ. Բաբայան[1,2]

[1]Հայաստանի ազգային պոլիտեխնիկական համալսարան, Գյուղատնտեսական թունաքիմիկատների սպացման և որակի վերահսկման բազային գիտահետազոտական լաբորատորիա

[2]ՀՀ ԳԱԱ «Հայբիոտեխնոլոգիա» ԳԱԿ, էկոլոգիական անվտանգություն լաբորատորիա

Տվյալ աշխատանքում ուսումնասիվրել են *Pseudomonas, Xanthomonas, Stenotrophomonas* բնական հողային շտամների հակաբիոտիկակայունությունը: Բացահայտվել է դրանց թվում բազմակայուն ներկայացուցիչների գերակայումը: Որոշ շտամների համար ուսումնասիրվել են պլազմիդներով պայմանավորված ռեզիստենտության և դրա կայունության պատճառները: հակաբիոտիկների մոդիֆիկացման *blaOXA-10, catB7, aac(6')II, aph(3')IV* գեների (հայտնաբերված կլինիկական *Pseudomonas* շտամներում) առկայությունը հայտնաբերվել է ուսումնասիրված բնական մանրէների ինչպես պլազմիդներում, այնպես և նուկլեոիդում: Հետազոտության արդյունքների համաձայն՝ գինեթթվի նոր սինթետիկ ածանցյալները արդյունավետ են, ուսումնասիրված բակտերիաներին պատկանող, կենդանիների և մարդու բազմակայուն պայմանական պաթոգենների և ֆիտոպաթոգեն ներկայացուցիչների դեմ: Նախնական ուսումնասիրությունների արդյունքների հիման վրա ցույց է տրվել դրանց պոտենցիալ էկոտոքսիկոլոգիական անվտանգությունը:

Բանալի բառեր. գինեթթու, միկրոպարարտանյութ, գյուղատնտեսական բույսեր, բույսերի աճի խթանիչ (ֆիտոստիմուլյատոր), խելացնող կոմպլեքսներ:

МУЛЬТИРЕЗИСТЕНТНОСТЬ ПОЧВЕННЫХ XANTHOMONAS, STENOTROPHOMONAS, PSEUDOMONAS И БОРЬБА С НЕЙ ПРИ ПОМОЩИ НОВЫХ ПРОИЗВОДНЫХ ВИННОЙ КИСЛОТЫ

Б.Г. Бабаян[1,2]

[1]*Национальный политехнический университет Армении (НПУА), базовая научно-исследовательская лаборатория получения сельско-хозяйственных ядохимикатов и контроля качества*

[2]*Научно-Производственный Центр (НПЦ) «Армбиотехнология» Национальной Академии Наук Республики Армения (НАН РА), лаборатория экологической безопасности*

В данной работе изучена антибиотик-резистентность природных почвенных штаммов *Pseudomonas, Xanthomonas, Stenotrophomonas*. Среди них, выявлено преобладание мультирезистентных представителей. Для некоторых штаммов исследованы причины опосредованной плазмидами устойчивости и ее стабильности. Присутствие генов модификации антибиотиков *blaOXA-10, catB7, aac(6') II, aph(3')IV* (встречающихся в клинических штаммах *Pseudomonas*) было обнаружено как на плазмидах, так и на нуклеоиде изученных нативных бактерий. Согласно результатам исследований, новые синтетические производные винной кислоты эффективны против мультирезистентных оппортунистических патогенов животных и человека и фитопатогенных представителей исследуемых бактерий. По результатам предварительного скрининга показана их потенциальная экотоксикологическая безопасность.

Ключевые слова: винная кислота, микроудобрения, сельскохозяйственные растения, стимулятор роста растений (фитостимулятор), хелатирующие комплекс.

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