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Oleksandr MASLOV
PhD, Assistant, Department of General Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002 (alexmaslov392@gmail.com)
***ORCID:** 0000-0001-9256-0934*

Mykola KOMISARENKO
PhD, Assistant, Department of Pharmacognosy and Nutriciology, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002 (a0503012358@gmail.com)
***ORCID:** 0000-0002-1161-8151*

Svitlana PONOMARENKO
PhD, Leader researcher of Laboratory of Biochemistry and Biotechnology, Mechnikov Institute of Microbiology and Immunology of the NAMS of Ukraine, Pushkinska str., 15, Kharkiv, Ukraine, 61002 (svponomarenko@i.ua)
***ORCID:** 0000-0002-1161-8151*

Tetiana OSOLODCHENKO
PhD, Head of Laboratory of Biochemistry and Biotechnology, Mechnikov Institute of Microbiology and Immunology of the NAMS of Ukraine, Pushkinska str., 15, Kharkiv, Ukraine, 61002 (imi_lbb@ukr.net)
***ORCID:** 0000-0001-7258-3880*

Sergii KOLISNYK
Doctor of Pharmaceutical Sciences, Professor, Head of Department, Department of General Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002 (kolesnik@nuph.edu.ua)
***ORCID:** 0000-0002-4920-6064*

Oleh KOSHOVYI
Doctor of Pharmaceutical Sciences, Professor, Institute of Pharmacy, Faculty of Medicine, University of Tartu, Nooruse str. 1, Tartu, Estonia, 50411 (oleh.koshovyi@gmail.com)
***ORCID:** 0000-0001-9545-8548*

Mykola GOLIK
Doctor of Pharmaceutical Sciences, Professor, Department of General Chemistry, National University of Pharmacy, Pushkinska str., 53, Kharkiv, Ukraine, 61002 (aptekar4009@gmail.com)
***ORCID:** 0000-0003-3134-9849*

Andrey KOMISSARENKO
Doctor of Pharmaceutical Sciences, Professor, Pharmaceutical Company "ZDRAVOPHARM", Uspenskaya str., 6, Sorokivka, Kharkiv region, 62430 (nik25spider@gmail.com)
***ORCID:** 0000-0002-2238-5138*

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INVESTIGATION ANTIMICROBIAL INTERACTION OF ARBUTIN AND ANTIBIOTICS OF DIFFERENT GROUPS AGAINST GRAM-NEGATIVE BACTERIA STRAINS

***Actuality**. The basic therapy against microbial infections is application antibiotics. However, overuse of antibiotics has become the major factor for the emergence and dissemination of multi-drug resistant strains.*

***The aim of the study** was investigate in vitro and in silico antimicrobial interaction of arbutin and antibiotics of different group against bacteria strains E. coli, P. aeruginosa, P. vulgaris.*

***Materials and methods**. The molecular docking was performed using AutoDockTools 1.5.6; antimicrobial effects were evaluated by the well method.*

Research results. *It has established that only levofloxacin, clarithromycin, azithromycin and arbutin were highly selective inhibition of all «targeted» antimicrobial mechanisms of gram-negative bacteria. Experimental results have shown that arbutin increased antimicrobial activity of antibiotics against P. aeruginosa, E. coli, P. vulgaris.*

Conclusion. *The study has demonstrated that antimicrobial interaction mechanism of arbutin with antibiotics was based on inhibition «targets», which were not covered by antimicrobial drugs. The highly effective antimicrobial drug against Gram-negative strains can be only a complex of "classical" antimicrobial drugs and herbal drug or dietary supplements based on extracts from arbutin-containing medicinal plants such as lingonberry, bearberry and cranberry should be used in treatment therapies.*

Key words: *arbutin, Gram-negative strains, molecular docking, antimicrobial interection, antibiotics*

Олександр МАСЛОВ
доктор філософії, асистент кафедри загальної хімії, Національний фармацевтичний університет, вул. Пушкінська, 53, м. Харків, Україна, 61002 (alexmaslov392@gmail.com)
ORCID: *0000-0001-9256-0934*

Микола КОМІСАРЕНКО
кандидат фармацевтичних наук, асистент кафедри фармакогнозії та нутриціології, Національний фармацевтичний університет, вул. Пушкінська, 53, м. Харків, Україна, 61002 (a0503012358@gmail.com)
ORCID: *0000-0002-1161-8151*

Світлана ПОНОМАРЕНКО
кандидат біологічних наук, старший науковий співробітник лабораторії біохімії та біотехнології, ДУ «Інститут мікробіології та імунології ім. І.І. Мечникова НАМН України», вул. Пушкінська, 15, м. Харків, Україна, 61002 (svponomarenko@i.ua)
ORCID: *0000-0003-3994-3500*

Тетяна ОСОЛОДЧЕНКО
кандидат біологічних наук, завідувач лабораторії біохімії та біотехнології, ДУ «Інститут мікробіології та імунології ім. І.І. Мечникова НАМН України», м. Харків, Україна, вул. Пушкінська, 15, м. Харків, Україна, 61002 (imi_lbb@ukr.net)
ORCID: *0000-0001-7258-3880*

Сергій КОЛІСНИК
доктор фармацевтичних наук, професор, завідувач кафедри загальної хімії, Національний фармацевтичний університет, вул. Пушкінська, 53, м. Харків, Україна, 61002 (kolesnik@nuph.edu.ua)
ORCID: *0000-0002-4920-6064*

Олег КОШОВИЙ
доктор фармацевтичних наук, професор, професор, Інститут фармації, факультет медицини, Університет Тарту, вул. Ноорузе. 1, Тарту, Естонія, 50411 (oleh.koshovyi@gmail.com)
ORCID: *0000-0001-9545-8548*

Микола ГОЛІК
доктор фармацевтичних наук, професор кафедри загальної хімії, Національний фармацевтичний університет, вул. Пушкінська, 53, м. Харків, Україна, 61002 (aptekar4009@gmail.com)
ORCID: *0000-0003-3134-9849*

Андрій КОМІСАРЕНКО
доктор фармацевтичних наук, професор, фармацевтична компанія «ЗДРАВОФАРМ», вул. Успенська, 6, м. Сороковка , Харківська область, 62430 (nik25spider@gmail.com)
ORCID: *0000-0002-2238-5138*

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ДОСЛІДЖЕННЯ АНТИМІКРОБНОЇ ВЗАЄМОДІЇ АРБУТИНУ ТА АНТИБІОТИКІВ РІЗНИХ ГРУП ПРОТИ ШТАМІВ ГРАМНЕГАТИВНИХ БАКТЕРІЙ

Актуальність. *Основною терапією проти мікробних інфекцій є застосування антибіотиків. Однак надмірне використання антибіотиків стало основним чинником появи та поширення мультирезистентних штамів.*

Мета дослідження *– вивчення in vitro та in silico антимікробної взаємодії арбутину та антибіотиків різних груп проти штамів бактерій E. coli, P. aeruginosa, P. vulgaris.*

Матеріал і методи*. Молекулярний докінг проводився за допомогою AutoDockTools 1.5.6; антимікробну дію оцінювали методом лунки.*

Результати дослідження. *Установлено, що лише левофлоксацин, кларитроміцин, азитроміцин і арбутин виявляли високоселективне пригнічення всіх «цільових» антимікробних механізмів грамнегативних бактерій. Результати експериментів показали, що арбутин посилює антимікробну активність антибіотиків проти P. aeruginosa, E. coli, P. vulgaris.*

Висновок. *Дослідження показало, що механізм протимікробної взаємодії арбутину з антибіотиками ґрунтується на інгібуванні «мішеней», які не підпадали під дію антимікробних препаратів. Високоефективним антимікробним препаратом проти грамнегативних штамів може бути лише комплекс «класичних» протимікробних препаратів та фітопрепарати або дієтичні добавки на основі екстрактів арбутин-вмісних лікарських рослин, таких як брусниця, мучниця, журавлина.*

Ключові слова: *арбутин, грамнегативні штам, молекулярний докінг, антимікробна взаємодія, антибіотики.*

Introduction. Actuality. Group of international researches have been estimated global mortality associated with bacterial infections. They have analyzed 343 million individual patient records and pathogen isolates, overall the researches have been estimated 13.7 million infection-related deaths in 2019, with 7.7 million associated with the 33 bacterial pathogens and 11 infectious syndromes studied. These deaths made up 13.6% of all global deaths and 56.2% of all sepsis-related deaths in 2019. The all-age mortality rate was 99.6 deaths per 100,000 population. Of the investigated pathogens, five – *Staphylococcus aureus, Escherichia coli, Streptococcus pneumoniae, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*–accounted for 54.9% of the 7.7 million deaths, with *S aureus* associated with more than 1.1 million deaths. *S. aureus* was the leading bacterial cause of death in 135 countries and was associated with the most deaths in people over 15 years (940,000). *S pneumoniae* was associated with the most deaths in children under 5 years (225,000), while *K. pneumoniae* was associated with the most newborn deaths (124,000). *Salmonella enteric*a serovar Typhi was linked to the most deaths in children ages 5 to 14 years (49,000). The study notes that these estimates would put these infections ahead of HIV, cancer, and self-harm as leading causes of death globally in 2019 (Ikuta, 2019, pp. 1–9).

Antibiotic resistance is the property of microorganisms to counteract the action of antimicrobial substances, and this phenomenon is associated with antibiotics losing their potency in inhibiting the growth of microorganisms (Pulingam, 2022, p. 106103). According to the 2021 report of the Global Antimicrobial Resistance and Use Surveillance System by the WHO, it was stated that bacteria such as *E. coli*, *S. aureus*, *Salmonella spp.*, *A. baumannii*, and *P. aeruginosa* are most prone to developing antibiotic resistance (Ajulo, 2024, p. e0297921). Treating infectious diseases caused by resistant bacteria incurs high medical service costs. According to World Bank data, by 2050, due to the development of antibiotic resistance, global capital could lose approximately $300 billion to $1 trillion. Furthermore, studies have shown that antibiotic resistance can lead to reduced labor productivity, population numbers, and quality of human capital, causing impoverishment in low– and middle-income countries (Jonas, 2017, p. 174). Thus, the search for new approaches to revive, implement, and produce antibiotics that have lost their effectiveness is currently crucial for the pharmaceutical industry and medicine worldwide.

Before the creation and use of antibiotics, people have applied drugs based on medicinal plants, such as lingonberry (*Vaccinium vitis-idaea* L.), bearberry (*Arctostaphylos uva-ursi* L.) and cranberry (*Vaccinium macrocarpon* L.) to treat infectious diseases (Maslov, 2023, pp. 77–82). The above-mentioned plants are a rich source of tannins, flavonoids, hydroxycinnamic acids and hydroquinone derivatives (Zhou, 2019, p. 3303). Arbutin is a main constituent among hydroquinone derivatives, it a β-D-glucopyranoside of hydroquinone presented in the medicinal plants of *Ericaceous* family (Nahar, 2022, p. 8786). (fig.) The leaves of the mentioned medicinal plants have been applied in folk medicine for treatment urinary infection diseases as cystitis, pyelonephritis and glomerulonephritis. The antimicrobial mechanism of arbutin still have not investigated in all details for today. However, recent research has shown that arbutin could destroy the bacterial membrane, influence of intracellular substances affects synthesis of proteins and inhibit DNA-gyrase (Ma, 2019, pp. 1291–1303).

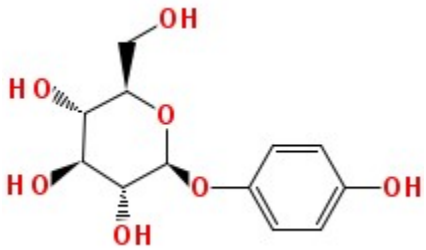

Fig. Structural formula of arbutin

The aim of our study – to investigate *in vitro* and *in silico* antimicrobial interaction of arbutin and antibiotics of different group against bacteria strains *E. coli*, *P. aeruginosa*, *P. vulgaris*.

Research materials and methods. ***Reagents***

Arbutin (≥98.0%) was purchased in Sigma Aldrich Company, Lublin, Poland; clarithromycin (≥98.0%); azithromycin (≥98.0%); gentamycin (≥98.0%); ciprofloxacin (≥98.0%); levofloxacin (≥98.0%); ceftriaxone (≥98.0%); chloramphenicol (≥98.0%) were provided by pharmaceutical company «Astrapharm» Kiev, Ukraine; and by pharmaceutical company «Zdravopharm», Kharkiv, Ukraine.

Test organisms

Museum strains of *Escherichia coli ATCC 25922*, *Proteus vulgaris NTCS 4636*, *Pseudomonas aeruginosa ATCC* 27853 were used in accordance with the recommendations for the assessment of antimicrobial activity of drugs».

Screening antimicrobial activity

The method of diffusion of the drug into agar carried out using the method of «wells» (Maslov 2022; Volyanskiy, 2004). Table 1 shows interpretation criteria for microbial sensitivity.

Molecular docking

A molecular docking study was conducted using the tool known as AutoDockTools 1.5.6 (Morris, 2008, pp. 1–9). The preparation of the protein involved an optimization process, which included the removal of water and other atoms, followed by the addition of a polar hydrogen group. Autogrid was used to configure the grid coordinates (X, Y, and Z) on the binding site. Genetic algorithm parameters were applied for ligand interaction, with 10 runs of this criterion.

Table 1

Interpretation criteria for microbial sensitivity

Microbial sensitivity	Diameter of the growth retardation zone, mm
High sensitivity	>25
Sensitive	15–25
Low sensitivity	10–15
Not sensitivity	<10

The theoretical investigation of antimicrobial activity against Gramm-negative strains was carried out against following enzyme structures of *P. aeruginosa*: DNA-gyrase (PDB ID: 1KIJ), DHFR (PDB ID: 1RX3), deacytelese (PDB ID: 3UHM). All structures were obtained from PDB database (RCSB PDB). The resolution of 1KIJ was 2.30 Å, 1RX3 – 2.20 Å, 3UHM – 2.20 Å, 1KZN – 2.30 Å, 3FRA – 2.35 Å, 3UHM – 2.26 Å. For docking experiment protein structure is selected if resolution above 2 Å. So, all mentioned proteins can be used for the experiment. The ligand structures of arbutin (CID_12303220), clarithromycin (CID_84029); azithromycin (CID_447043); gentamycin (CID_3467); ciprofloxacin (CID_2764); levofloxacin (CID_149096); ceftriaxone (CID_5479530); chloramphenicol (CID_5959) were obtained from PubChem database (PubChem). The active site of the docking protein was identified utilizing the Computed Atlas for Surface Topography of Proteins (CASTp).

Research results and their discussion. A theoretical investigation of the antimicrobial activity of the arbutin and antibiotics were carried out using molecular docking, in order to understand their promising capabilities for suppressing the growth of Gram-negative strains of bacteria. The assessment the antimicrobial effect was conducted with 3 key enzymes of «first line of defense» for Gram-negative strains: DNA-gyrase, DHFR, Deacytelese. A six groups of the most applied antimicrobial drugs were chosen as standards of comparison in theoretical study such as a group of aminoglycosides (Gentamycin), fluoroquinolones (Ciprofloxacin, Levofloxacin), β-lactames (Ceftriaxone), amphenicols (Chloramphenicol), macrolides (Clarithromycin, Azithromycin) and 5-nitroimidazole drugs (Metronidazole, Ornidazole).

In the indexed scientific journals Scopus and Web of Science, there are a large number of works with molecular docking on the study of the pharmacological activity of different groups of compounds. But, the main problem of these studies is the lack of rating assessment of the efficiency of binding of the ligand to the active site. A number of scientific works have used comparison standards, but in our view, this method is not promising as since more than one standard may be used for the enzyme protein being studied. Thus, this method of assessment will lead to confusion in the data among scientists. To understand the level of selectivity of inhibition of the studied substances to the active centers of bacterial enzymes, we applied the following classification of selectivity (Kondža, 2024, pp. 644): IC50 < 0.001 mM (high selective); 0.05 > IC50 > 0.01 (medium selective); IC50 >0.05 mM (low selective).

Molecular modeling of the identified compounds was carried out with the active site of DNA-gyrase. The active site was represented by the following amino acids: Arg75, Lys102, Arg135, Asp80. Trp387, Lys109, Asp72 and Thr166. According to the results of the study and conditional rating of selectivity, it was established that clarithromycin, azithromycin, levofloxacine and arbutin were high selective to the active site, whereas ciprofloxacin, chloramphenicol was medium selective and ornidazole, ceftrioxane, metronidazole, gentamycine were low selective (table 2).

The next enzyme that was studied was DHFR. The active center of this enzyme was represented by the following amino acids: NADP, Tyr110, Asp30, Ile8, Phe34, Ile104, Arg55, Arg60. According to the results shown in table 3, the following compounds had high selectivity: clarithromycin, azithromycin, levofloxacine and arbutin, whereas ornidazole, metronidazole were low selective.

Molecular modeling of the studied compounds was carried out with the active site of Deacytelese. The active center was represented by the following amino acids: Thr190, Lys238, Gly92. Phe191, Leu18, Ala206. According to the results of the study and conditional classification, it was established that clarithromycin, azithromycin, levofloxacine and arbutin had the highest selectivity, whereas ornidazole, metronidazole had the lowest selectivity (table 4).

Further, all antibiotics and arbutin were conditionally divided into two categories. The first category included compounds that had a high selectivity for the active site, and the second category included compounds that had medium and low selectivity. This compound separation approach was necessary to clearly identify compounds that interact highly effectively with antimicrobial mechanisms and which compounds work below this level. According to the results shown in Table 5, there was only four compounds that inhibited all mechanisms against Gram-negative strains – clarithromycin, azithromycin, levofloxacin, arbutin. The next antibiotic that inhibit high selectively antibacterial mechanisms against Gram-negative strains was ciprofloxacin. (Comparing with antibiotics standards, arbutin were hit all «targets» antibacterial mechanisms of the "first line of defense" of Gram-negative bacteria (table 5).

Table 2

Results of molecular docking of the arbutin, and antimicrobials drug standards with the DNA-gyrase structure of *P. aeruginosa*

№	Ligand	DNA-gyrase		
		ΔGbind[a] (kcal/mol)	Ki[b] (mmol)	Level of selectivity
1.	Clarithromycin	**-11.59**	0.00000001087	High selective
2.	Azithromycin	**-10.29**	0.00000061435	High selective
3.	Levofloxacin	**-8.69**	0.00042853	High selective
4.	Arbutin	-8.23	0.00093344	High selective
5.	Ciprofloxacin	**-8.06**	0.00123	Medium selective
6.	Chloramphenicol	**-6.38**	0.02114	Medium selective
7.	Ornidazole	**-5.07**	0.19214	Low selective
8.	Ceftriaxone	**-4.61**	0.41631	Low selective
9.	Metronidazole	**-4.54**	0.46734	Low selective
10.	Gentamycin	**-4.08**	1.03	Low selective

Note: a – free-binding energy; b – inhibition constant, IC50, mmol

Table 3

Results of molecular docking of the arbutin and antimicrobials drug standards with the DHFR structure of *P. aeruginosa*

№	Ligand	DHFR		
		ΔGbind[a] (kcal/mol)	Ki[b] (mmol)	Level of selectivity
1.	Clarithromycin	-16.78	0.000000000504	High selective
2.	Azithromycin	**-14.50**	0.00000002336	High selective
3.	Arbutin	-9.17	0.00019023	High selective
4.	Levofloxacin	**-8.98**	0.00026376	High selective
5.	Ciprofloxacin	-8.44	0.00064808	High selective
6.	Chloramphenicol	**-7.97**	0.00143	Medium selective
7.	Gentamycin	**-6.78**	0.01073	Medium selective
8.	Ceftriaxone	**-6.36**	0.02164	Medium selective
9.	Ornidazol	-4.95	0.23625	Low selective
10.	Metronidazole	**-4.28**	0.72416	Low selective

Note: a – free-binding energy; b – inhibition constant, IC50, mmol

In order to inhibit the growth of any bacteria, you need to effectively influence 3 main mechanisms: DNA gyrase, DHFR and inhibition of membrane formation. DNA gyrase is an enzyme responsible for the temporary division of bacterial DNA into two strands, subsequently the replication stage begins (Jadhav, 2017, pp. 1–9)). The next important enzyme is DHFR; this enzyme is responsible for the formation of folic acid, which is necessary for the existence of bacteria (Mbarga, 2021; Rahman, 2020). One of the main defense mechanisms of any bacteria is its membrane, and gram-negative strains are no exception to the rule. The membrane of gram-negative bacteria contains a special liposaccharide that causes an immune system response and fever. The enzyme UDP-3-O-(R-3-hydroxymyristoyl)-N-acetylglucosamine deacetylase is responsible for the synthesis of liposaccharide; this enzyme has no homologs in humans and mammals and is present only in bacteria (Zuo, 2017; Bertonha, 2023). According to the results obtained, it was found that only three out four of the investigated antibiotics and arbutin highly selectively inhibits all «targets» mechanisms of antimicrobial action against Gram-negative strain.

In this research work, the antimicrobial activity of the arbutin, antibiotics and their combination at one concentration was investigated against the following Gram-negative strains of *P. aeruginosa, E. coli, P. vulgaris*. According to the obtained results, all Gramm-negative strains of bacteria were sensitive to the action of arbutin.

All the studied antibiotics inhibited the growth of *P. aeruginosa*, *E. coli*, and *P. vulgaris*. In studies of combinations of arbutin and antibiotics at the same molar concentration of 0.003 mM, an increase in the antimicrobial activity of antibiotics was observed, ranging from 3 to 35% against *P. aeruginosa*. The highest increase in inhibitory activity was observed with ornidazole (+33%), metronidazole (+35%), clarithromycin (+20%), and gentamicin (+17%). In studies of the antimicrobial activity of combinations of arbutin with antibiotics against *E. coli*, it was found that arbutin enhanced the action of antibiotics by 3 to 37%. A significant increase in antimicrobial activity was observed with chloramphenicol (+37%), metronidazole (+35%), ornidazole (+30%), and ceftriaxone (+16%). In the case of

Table 4

Results of molecular docking of the arbutin and antimicrobials drug standards with the deacytelese structure of *P. aeruginosa*

№	Ligand	Deacytelese		
		ΔGbind[a] (kcal/mol)	Ki[b] (mmol)	Level of selectivity
1.	Azithromycin	**-14.04**	0.000000051	High selective
2.	Clarithromycin	**-13.98**	0.000000057	High selective
3.	Levofloxacin	**-8.34**	0.00077565	High selective
4.	Arbutin	-8.40	0.00070067	High selective
5.	Ciprofloxacin	**-7.51**	0.00313	Medium selective
6.	Chloramphenicol	**-7.19**	0.00536	Medium selective
7.	Gentamycin	**-7.45**	0.00346	Medium selective
8.	Ceftriaxone	**-6.09**	0.03444	Medium selective
9.	Ornidazole	**-5.32**	0.12638	Low selective
10.	Metronidazole	**-5.20**	0.15555	Low selective

Note: a – free-binding energy; b – inhibition constant, IC50, mmol

Table 5

Schematic division of antimicrobial drug standards and arbutin in two categories

№	Compound	Gram-negative strains (P. aeruginosa, E. coli, P. vulgaris)			Gram-negative strains
		DNA-gyrase	DHFR	Deacytelese	№ of inhibition enzymes of «First line of protection»
1	**Clarithromycin**				3
2	**Chloramphenicol**				0
3	**Ciprofloxacin**				1
4	**Levofloxacin**				3
5	**Ceftriaxone**				0
6	**Metronidazole**				0
7	**Ornidazole**				0
8	**Gentamycin**				0
9	**Azithromycin**				3
11	Arbutin				3

Note: green colour – high level of selectivity; red colour – lower and medium of selectivity

P. vulgaris, it was found that arbutin enhances the action of antibiotics by 3 to 100% (table 6).

Our studies have shown that arbutin in combination with "classical" antibiotics enhances the antimicrobial effect against Gram-negative bacteria. This phenomenon can be justified as follows: to suppress the growth of bacteria, there are a number of key enzymes that are important for the life and development of bacteria; in turn, antibiotics are able to actively inhibit only part of the mechanisms for which antibiotics are highly selective, while other "targets" remain in active states. When arbutin is added, all enzymes are completely suppressed, which ultimately leads to the death of bacteria. For example, according to theoretical studies, gentamicin is a moderately selective inhibitor in relation to DHFR, and in the case of DNA gyrase and deacetylase, it is a low-selective inhibitor, while arbutin is a highly selective inhibitor for DNA gyrase. In experimental studies, antimicrobial activity was shown to increase by 17, 8 and 15% for *P. aeruginosa*, *E. coli* and *P. vulgaris*, respectively. We can observe this dependence in the case of other antibiotics in relation to Gram-negative bacteria.

However, it was found that the enhancement of antimicrobial activity was not even higher than 10%. In our opinion, this phenomenon is due to the fact that the antibiotic and arbutin have the same mechanisms of action and their antimicrobial activity overlaps and does not have such a high increase in effect as in the case of metronidazole and ornidazole. We can substantiate this phenomenon using the example of levofloxacin. Both compounds arbutin and levofloxacin are highly selective inhibitors of all three "targets" of Gram-negative bacteria. Experimental studies showed that the enhancement effect was only 5, 6 and 3% relative to *P. aeruginosa*, *E. coli* and *P. vulgaris*, respectively. However, clarithromycin is not subject to this dependence; according to our theoretical studies, it

Table 6

Inhibition diameter (mm) resulting from the screening of antimicrobial effect against strains of *P. aeruginosa, E. coli* and *P. vulgaris* by well diffusion method with arbutin, antibiotic standards

Sample	Concentration, mM	Diameter of the growth retardation zone, mm±SD					
		P. aeruginosa	Difference,%	E. coli	Difference,%	P. vulgaris	Difference, %
Arbutin	0.003	16.00±0.20		17.00±0.20		14.00	
Clarithromycin	0.003	**14.00±0.20**		22.00±0.20		14.00±0.20	
Arbutin+ **Clarithromycin**	0.003+0.003	**18.00±0.20**	+20%	26.00±0.20	+12%	19.00±0.20	+21%
Arbutin	0.003	16.00±0.20		17.00±0.20		14.00±0.20	
Azithromycin	0.003	**21.00±0.50**		25.00±0.20		21.00±0.20	
Arbutin+**Azithromycin**	0.003+0.003	**24.00±0.50**	9%	**27.00**±0.20	+7%	23.00±0.20	+9%
Arbutin	0.003	16.00±0.20		17.00±0.20		14.00**±0.20**	
Chloramphenicol	0.003	**16.00±0.20**		16.00±0.20		15.00±0.20	
Arbutin+ **Chloramphenicol**	0.003+0.003	**17.50±0.50**	+9%	26.00±0.20	+37%	19.0±0.200	+21%
Arbutin	0.003	16.00±0.20		17.00±0.20		14.00**±0.20**	
Ciprofloxacin	0.003	**30.00±0.20**		29.00±0.20		29.00±0.20	
Arbutin+ **Ciprofloxacin**	0.003+0.003	**31.00±0.20**	+3%	30.00±0.20	+3%	30.00±0.20	+3%
Arbutin	0.003	16.00±0.20		17.00±0.20		14.00**±0.20**	
Levofloxacin	0.003	**29.00±0.20**		31.00±0.20		30.00±0.20	
Arbutin+ **Levofloxacin**	0.003+0.003	**31.00±0.20**	+5%	33.00±0.20	+6%	31.00±0.20	+3%
Arbutin	0.003	20.00±0.20		17.00±0.20		14.00**±0.20**	
Ceftriaxone	0.003	**30.00±0.20**		27.00±0.20		24.00±0.20	
Arbutin + **Ceftriaxone**	0.003+0.003	**32.00±0.20**	+6%	32.00±0.20	16%	30.00±0.20	+18%
Arbutin	0.003	16.00±0.20		17.00±		13.00±0.20	
Metronidazole	0.003	**12.00±0.20**		15.00±0.20		Growth	
Arbutin+ **Metronidazole**	0.003+0.003	**19.00±0.50**	+35%	24.00±0.20	+35%	19.00±0.20	+100%
Arbutin	0.003	16.00±0.20		17.00±0.20		14.00**±0.20**	
Ornidazole	0.003	**12.00±0.20**		16.00±0.20		Growth	
Arbutin+ **Ornidazole**	0.003+0.003	**18.00±0.20**	+33%	23.00±0.20	+30%	19.00±0.20	+100%
Arbutin	0.003	16.00±0.20		17.00±0.20		14.00**±0.20**	
Gentamycin	0.003	**26.00±0.20**		27.00±0.20		26.00±0.20	
Arbutin+ **Gentamycin**	0.003+0.003	**32.00±0.20**	+17%	30.00±0.20	+8%	31.00±0.20	+15%

Note: SD – standard deviation, n=3

was shown that clarithromycin is the leader among highly selective inhibitors; if arbutin is added, the antimicrobial effect of clarithromycin against Gram-negative bacteria increases from 12 to 21%. We hypothesize that this is due to the fact that arbutin is a highly selective inhibitor of another mechanism that clarithromycin cannot actively inhibit, for example, the 50S ribosomal subunit.

This method of interaction can be used to "bring back to life" antimicrobial drugs that have lost their effectiveness for today. Because the creation and development of new antibiotics is a time-consuming and expensive investment. In addition to the above, we would like to note that arbutin, when compared with other antibiotics such as metronidazole, ornidazole, gentamicin, ceftriaxone, has minimal side effects. High doses of arbutin are not possessed nephrotoxicity, ototoxicity and hepatotoxicity as antibiotics from the group of aminoglycosides, cephalosporins and 5-nitroimidazoles.

Based on the above results, we can conclude that in order to obtain a highly effective antimicrobial drug against Gram-negative strains, a complex of "classical" antimicrobial drugs and herbal drug or dietary supplements based on extracts from arbutin-containing medicinal plants such as lingonberry, bearberry and cranberry should be used in treatment therapies.

Conclusion

These investigation have shown that only levofloxacin, clarithromycin, azithromycin and arbutin were highly selective inhibition of all «targeted» antimicrobial mechanisms of gram-negative bacteria. Experimental results have shown that arbutin increased antimicrobial activity of antibiotics against *P. aeruginosa*, *E. coli*, *P. vulgaris*. The study demonstrated that interaction mechanism of arbutin was based on inhibition «targets», which were not covered by antimicrobial drugs. The highly effective antimicrobial drug against Gram-negative strains can be only a complex of "classical" antimicrobial drugs and herbal drug or dietary supplements based on extracts from arbutin-containing medicinal plants such as lingonberry, bearberry and cranberry should be used in treatment therapies.

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Komissarenko A.M. – methodology, conclusions.

Email address for correspondence with the authors: *alexmaslov392@gmail.com*