

REVIEW

for dissertation work

WU LIN

on the subject

"RESISTANCE FACTORS OF BACTERIAL NOSOCOMIAL INFECTIONS CAUSATIVE AGENTS AS BACKGROUND FOR THE MODERN ANTIMICROBIALS DEVELOPMENT",

presented for obtaining the degree of Doctor of Philosophy

in the field of knowledge 09 - Biology

specialty 091 – Biology

Relevance of the dissertation topic

The topic of the dissertation is relevant, due to the fact that antibiotic resistance is an extremely widespread problem that is relevant for everyone. There is no doubt that the most important reason for the acquisition of antibiotic resistance by bacteria is the widespread and uncontrolled use of antibiotics themselves and their improper disposal. Due to the resistance of bacteria to antibiotic therapy, the fight against infectious diseases becomes more difficult. Effective treatment of infections caused by antibiotic-resistant microorganisms is possible when based on the analysis of data about the pathogen. These are data on sensitivity to drugs and markers of resistance.

Evaluation of the validity of the scientific results of the dissertation, their reliability and novelty

The scientific novelty of the results of the dissertation research is as follows:

The following scientific results were obtained for the first time in the dissertation:

- on the basis of genome sequencing and gene annotation of the strain *Bacteroides thetaiotaomicron* DSMZ 2079 isolated from the patient's blood, the presence of a one- and two-component system for recognizing environmental signals and responding to them was shown, the presence of four homologs of the self-transmitted conjugative transposon CTnDOT, which provides the extension of resistance to tetracycline and erythromycin. The *rpoB* and *tuf* genes were identified (in the JHR92_RS03155 and JHR92_RS03195 loci, respectively), which determine the strain's resistance to antibiotics;

- based on the results of the analysis of the 16S rRNA sequences of the isolated clinical strain *Pseudomonas oryzihabitans* JN 873340 and its comparison with 29 other strains of the species from GenBank, a phylogenetic tree was built and the possibility of identifying their geographical origin by two hypervariable regions V4 and V5 was shown;

- minimum inhibitory concentrations of the new antibiotic streptofungin against *C. albicans* ATCC 10231 (10 µg/ml), *B. subtilis* ATCC 6633 (200 µg/ml) and *P. aeruginosa* ATCC 9027 (500 µg/ml) were established, as well as the absence of toxicity in a wide range of concentrations (from 2.5 to 500 µg/ml), which determines its potential as an active pharmaceutical ingredient.

Scientific research was carried out by the recipient at the department industrial biotechnology and biopharmacy KPI named after Igor Sikorsky and at the Environmental Comprehensive laboratory of Hainan Medical University, Haikou (China).

So, in the dissertation, the scientific task justification of systemic approaches to the development of modern antimicrobial drugs based on the analysis of resistance factors of bacterial pathogens of nosocomial infections completed in full, the recipient has fully mastered the methodology of scientific activity.

Assessment of the content of the dissertation, its completeness and compliance with the principles of academic integrity.

According to its content, the applicant's dissertation work Wu Lin fully meets the Standard of higher education in the specialty 091 – Biology and areas of research in accordance with the educational program «Applied biology».

The dissertation is a completed scientific work and testifies to the presence of the applicant's personal contribution to the scientific direction «Applied biology».

Having considered the similarity report based on the results of checking the dissertation work for text matches, it can be concluded that the dissertation work Wu Lin is the result independent research of the acquirer and does not contain elements of falsification, compilation, fabrication, plagiarism and borrowing. Used ideas, results and texts of other authors have appropriate references to the relevant source.

Language and style of presentation of results

The dissertation is written in English.

The material of the dissertation is laid out logically and consistently, using commonly used scientific terminology.

The dissertation consists of an introduction, 5 chapters, conclusions, a list of references and appendices. The total volume of the dissertation is 144 pages.

In the introduction demonstrates the relevance of the topic of the dissertation research, its connection with scientific programs, plans, topics, goals, tasks, the subject and object of the work, the research methods used, the scientific novelty and practical significance of the results obtained, the personal contribution of the applicant, the approval of the dissertation materials, structure and scope of work.

In the first chapter presents an analytical review of the sources on the topic of the dissertation: described nosocomial infections: pathogenicity, resistance and promising antimicrobials, as well as a description of *Streptomyces*, which act as the producers of antimicrobial substances.

In the second chapter is devoted to materials, technologies and methods studies used in the work: isolated microbial pathogen culture, strains and media. The following methods are described in detail: of identification of clinical strains and drug sensitivity test, PCR, sequence analysis, bioinformation analysis, construction of pKFS/LPETG vector and transformation, fluorescence assay, antagonistic activity determination, determining of the minimum inhibitory concentration, determining the cytotoxicity of antibiotic preparation, electron microscopy, biosynthesis, preparing and analyzing the activity of developed antimicrobial drugs and statistical methods.

In the third chapter presents the results research and control of the distribution and resistance factors of the bacterial nosocomial infections bacterial nosocomial infections causative agents. Conclusions for the section are formulated.

The fourth chapter describes the results of the screening of new antimicrobial substances and their characteristics. Conclusions for the section are given.

In the fifth chapter it is given antimicrobials based on substances from *Streptomyces albus* and recommendations for the implementation of monitoring the resistance of nosocomial infections and the principles of modern antimicrobial drugs work out. Conclusions for the section are given.

The dissertation was prepared in accordance with the requirements of the order of the Ministry of Education and Culture of Ukraine dated January 12, 2017 No. 40 "On approval of requirements for the preparation of the dissertation".

Publication of the results of the dissertation work.

The main provisions of the work are presented in 10 scientific papers: 4 scientific articles included in the Scopus scientometric database, including 2 of them in publications assigned to the 2nd quartile (Q2) in accordance with the SCImago Journal and Country Rank classification (equal to two publications that are counted in accordance with the first paragraph of paragraph 11 of the Resolution of the Cabinet of Ministers of Ukraine dated March 6, 2019 No. 167) ; 4 articles in specialized foreign periodicals; 2 theses at all-Ukrainian and international conferences.

The results of the work presented in the dissertation were obtained by the author personally or with his direct participation. Planning of the work and discussion of the results was carried out jointly with the academic supervisors. All publications adhere to the principles of academic integrity. The received conclusion of the commission certifies that the work was carried out in compliance with the principles of bioethics and can be recommended for submission to the defense.

Thus, the scientific results described in the dissertation are fully covered in the scholar's publications.

Disadvantages and comments to the dissertation work.

1. The list of materials does not include cell lines MDBK and A549, and the institution from which they were obtained, the use of which is specified in point 2.2.11, is not indicated.

2. In the description of Figure 4.2, there is a mention of the fluorescence signal of LPXTG-EGFP proteins was measured at 0 h (yellow), but why is the peak of this color not marked in the figure?

3. When presenting some tables and moving their parts to the following pages, it would be necessary to indicate "table continuation" and repeat the names of the columns, for example in the table. 2.1.

4. Why was the culture of *Pseudomonas oryzihabitans* chosen for the study, and not the more common pathogen of this genus, *Pseudomonas aeruginosa*?

5. There are separate technical mistakes in the work, for example in the formula on page 54 (ml, cm³, cm).

I believe that the comments expressed are not decisive and do not reduce the general scientific novelty and practical significance of the results and do not affect the positive evaluation of the dissertation work.

Conclusion on the dissertation work

I believe that the dissertation work of a candidate for the degree of Doctor of Philosophy Wu Lin on the topic " Resistance factors of bacterial nosocomial infections causative agents as background for the modern antimicrobials development – qualification scientific work on manuscript rights" performed at a high scientific level, does not violate the principles of academic integrity and is a completed scientific study, the set of theoretical and practical results of which solves a scientific task that is of significant importance for «Biology». The dissertation work in terms of relevance, practical value and scientific novelty fully meets the requirements of the current legislation of Ukraine, which are provided for in clauses 6 - 9 of the " Procedure for awarding the degree of Doctor of Philosophy and annulment of the decision of the one-

time specialized academic council of the institution of higher education, scientific institution on awarding the degree of Doctor of Philosophy" , approved by Resolution No. 44 of the Cabinet of Ministers of Ukraine dated January 12, 2022.

The acquirer Wu Lin deserves to be awarded the degree of Doctor of Philosophy in the field of knowledge 09 – Biology with the specialty 091 – Biology.

Reviewer:

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of Translational Medical Bioengineering
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