Biosafety and Biosafety of Health and the Environment on the Basis of Information Technologies

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Abstract
An abstract logical and comparative analysis of the use of alternative methods using information technologies and computer methods of molecular modeling and analysis of “structure-activity” relationships in the construction of safe biosubstances with the preservation of a safe environment in the production of drugs and products was conducted. The possibility of bioremediation of pollutants based on data from literary sources and experimental synthesis and screening of bioactivity of substances for their introduction into technological processes of the food, pharmaceutical and chemical industry with the possible utilization of waste through bioremediation was investigated.

Keywords 1
biosafety, bioremediation, bioactivity prediction, biologically active substances, biotesting, bioutilization, bioactivity screening.

1. Introduction

The current state of scientific research projects of biotechnology and commercial bioindustry in Ukraine regarding the development of bioengineering, as well as the level of development of biotechnological products production, requires innovative ways of safe research, biosafe latest technologies for the production, consumption and disposal of bioproducts waste, as side effects or double use of such technologies are possible and products often become a source of public fears, the subject of polar discussions and protests. Such a situation arises due to possible biothreats in the case of unprofessional or criminal use of advances in pharmaceuticals, agriculture, food and other sectors of the economy.

Scientific inquiries regarding the determination of the relationship between bioactivity and the structure of compounds in the development of new synthetic or bioengineering agents (medical, veterinary, and agricultural) obtained by various methods are relevant to this day [1]. methods, among which the evaluation of the acute toxicity of the products is carried out on laboratory animals in vivo [2]. However, such experimental studies are quite valuable, in addition, they are constantly criticized for ethical reasons. Therefore, since 2007, documents have been developed, in particular the Guidelines of the European Community on chemicals and their safe use (REACH), which provide for the development of computerized methods for analyzing "structure-activity" relationships and studying toxic effects [3]. In the light of solving this problem, the importance of using information technologies for the determination of pollutants and toxins in the monitoring of the environment and the safety of ecosystems for human health cannot be ignored.

ITTAP’2022: 2nd InternationalWorkshop on Information Technologies: Theoretical and Applied Problems, November 22–24, 2022, Ternopil, Ukraine
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The main purpose of the work it is the identification of promising bioactive substances and the search and development of ways to eliminate pollutants and toxins on the basis of information technologies using computer modeling of the bioactivity of compounds to create and real load the most common pollutants, taking into account the principles of sustainable development.

2. Results and methodology

2.1. Methodology

In the research process, a number of methods were used: abstract-logical (to generalize the methods of assessing the impact of harmful substances of enterprises on the environment), analysis and synthesis (to determine a comprehensive index of assessment of negative impacts), systemic analysis (to develop a system of pollution prevention measures). To predict the bioactivity of substances of potential drugs, a study was conducted using online resources SwissTargetPrediction and SuperPred and Molinspiration Cheminformatics [4,5,6]. To characterize the level of pollution in ecosystems, we used the results of our own research, as well as data from the literature. In experimental studies during biotesting and bioengineering of bioobjects, simulations of the real load of the most common pollutants, in particular nitrogen-containing ones, were carried out on the basis of biocomputing, which made it possible to find and develop ways to eliminate such pollution and toxins by complex bioremediation.

2.2. Results

In the analysis of data on the use of information technologies in the design of drugs and in the utilization of pollutants from industrial and household waste showed the need for new innovative approaches to the careful study and implementation of mathematical modeling and forecasting in the study of the bioactivity of substances and the performance of biotests in the study of biological objects at laboratory, pilot and production locations taking into account the dual use of biosafety results, knowledge of means of protection and elimination of biorisks in the production and consumption of bioproducts. This is required by the sphere of production and the sphere of the market of consumption and use of products of chemical, pharmaceutical or biological origin [7].

The development of effective bioactive substances for pharmaceuticals, agricultural technology, veterinary medicine and food technology is a long process and requires enormous financial costs. The majority of biosubstances were discovered as a result of systematic optimization of lead compounds that were found when testing substances on animals *in vivo*, isolated organs or *in vitro* on models of enzyme inhibition or binding to receptors. At the same time, one discovered biosubstance accounts for hundreds of thousands, or even more, of studied compounds [8]. Therefore, nowadays, the initial stage of *leader-compound* search among the data of combinatorial libraries of biologically active compounds is the use of pre-experimental *in silico* methods, in particular, virtual screening [9]. Since the initial data for such screening are only chemical structures and calculated properties of compounds, it can be applied to virtual libraries of almost any size.

For pharmaceuticals, the use of "*drug-like*" characteristics in the search for potential candidates for a medicinal substance and the prediction of the biological activity of compounds using the Molinspiration Cheminformatics internet service should be singled out as effective methods of virtual screening. The term "*drug-like characteristics*" began to be widely used after the publication of the work of Lipinski and colleagues [10]. It covers the concept of some characteristics of the structure of compounds that affect their biological effect and are related to properties that affect adsorption, distribution, metabolism, excretion and toxicity.

Based on the observations that most medicinal substances are relatively small and lipophilic molecules, Lipinski formulated empirical rules (Lipinski's rules or "*rule of five*") [10]. These rules are a set of molecular descriptors obtained on the basis of the analysis and classification of key physicochemical properties of medicinal products and biologically active compounds

Each of the parameters (Fig. 1) characterizes certain features of the structure. Molecular mass is a parameter related to the size of the molecule. Lipophilicity characterizes the distribution of the substance between the aqueous and lipid phases in the body and the ability of the substance to pass through the cell membrane. Parameters C and D indicate the ability of the compound to form, as a rule, hydrogen bonds, at the "*appropriate*" site of the biomolecule. Parameter E characterizes the "*stiffness*" of the structure and indicates the volume of the bound substance.

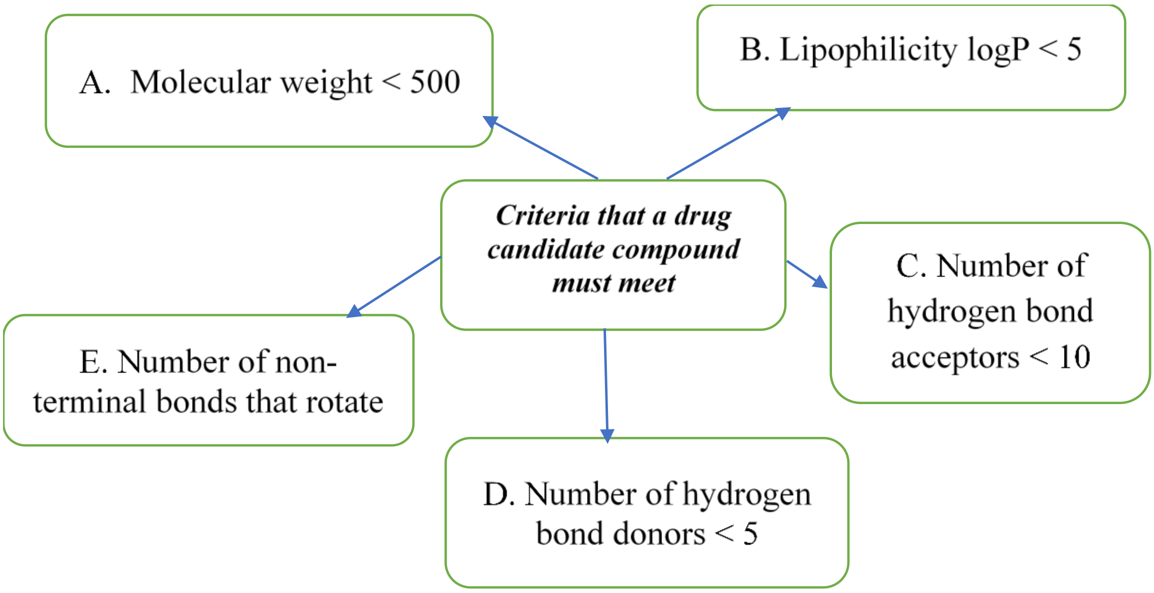

Figure 1: Lipinski's rules

One of the ways to assess the potential of natural and synthetic molecules (real or virtual) as biosubstances for safe protection of health or the environment is to determine their molecular targets. At the same time, the search for new targets for existing biosubstances using information technologies, as opposed to traditional experimental methods, can expand the limits of the application of these substances in a shorter time and at a lower cost. On the other hand, newly discovered molecular targets of existing biosubstances may involve potential side effects and drug toxicity, so efforts should be made to improve the safety of these substances. Experimental methods for identifying targets from in vivo are extremely time-consuming, expensive, and sometimes unsuccessful, because their implementation requires the development of effective experiments of biochemical and genetic interaction [11].

The currently available *in silico* bioactivity prediction approaches can be broadly classified into three groups: based on ligands (chemically similar compounds exhibit similar biological activity), based on structure (use of available three-dimensional 3D structures of targets to assess the structural and chemical suitability of the requested compound to the target) and hybrid.

Examples of ligand-based methods include *SEA*, *SuperPred*, *PASS*, and *TarPred*. To improve prediction performance, new techniques have emerged that use supervised (such as HitPick and Target Hunter) and unsupervised machine learning (ML) (such as SPiDER) to improve model accuracy. In addition, some of the previous methods, such as *ChemProt* and *SwissTargetPrediction*, have also updated their search engines to use ML models that have shown better performance

Research of bioactivity and safety of substances on the basis of information technology is widely used by the *Department of Technology of Biologically Active Compounds, Pharmacy and Biotechnology of Lviv Polytechnic National University* in scientific areas and projects. as an alternative to traditional methods, it was possible to establish the bioactivity of chemical compounds. The use of pre-experimental in silico methods of studying the bioactivity of chemical substances allowed scientists to optimize the search for promising substances among a large array (over 500) of thiosulfonate, quinone-containing and heterocyclic structures synthesized at the department [12, 13], to classify compounds into biologically active (*hit-compound*), similar to substance activity (*analog-compound*) and basic compounds with certain activity (*leader-compound*), and quickly and efficiently select promising leader compounds for further experimental in-depth biological research. In particular, the screening of the biological activity of newly synthesized compounds by microbiological and physiological methods (1BT screening - the study of many substances in one biological test and SBT test - the determination of two or three substances in a series of biological tests), which make it possible to confirm the results of virtual biological screening.

Molinspiration Cheminformatics SuperPred and *SwissTargetPrediction* online resources were used in the studies of predicting the biological activity of synthesized compounds.

SwissTargetPrediction is a web tool that allows you to predict the most likely protein targets for small molecules based on the principle of similarity using reverse screening [4].

SuperPred is a web server for predicting the bioactivity of compounds according to the anatomic-therapeutic chemical classification system proposed by WHO, for obtaining information about compounds in the process of drug development [5].

Evidence of the effectiveness of these alternative technologies are the patented biosubstances discovered with their help and confirmed by experimental research, in particular, an antitumor substance [14], an antithrombotic substance [15], a veterinary drug [16], a restegulator and a biocide for combating phytopathogenic microflora during phytoremediation of oil-contaminated soils [17] and a number of substances (for the design of drugs, for the protection of agricultural products from phytopathogens, for the purification of the aquatic ecosystem, for the bioutilization of waste) that are undergoing preclinical and clinical trials or are at the patenting stage.

Scientific research in biotechnology and bioengineering, as well as the technology of pharmaceutical preparations, involves understanding the peculiarities of compliance with safety standards during laboratory experimental research and production processes, as well as the need to comply with bioethical and biosafety principles in the scientific and industrial sphere, the introduction of the basic principles of biosecurity regulation in the field of biotechnology, as well as the use of materials and methods that may cause an unforeseen danger of dual use and have a negative impact on human safety and the environment

Biosafety problems, deepened by the lack of fundamental knowledge, imperfect modern technologies of production and waste disposal, since any productions are potential sources of pollution, especially the water and air ecosystem.

The biosecurity of the use of aquatic bioresources in the discharge of wastewater on the scale of small towns deserves special attention, taking into account the economic and climatic conditions of Ukraine. It is considered promising to treat wastewater using biotechnological methods that do not require significant costs and can be applied on a large scale to save energy and obtain useful products (environmentally friendly fertilizers, biogas, etc.), and the use of computer models of information technologies would provide an opportunity to strengthen the complex bioremediation of the ecosystem by obtaining virtual forecasts of the safety of wastewater pollution of enterprises with further modeling of cleaning methods and correlation with the obtained experimental data.

The most acceptable today are the methods of cleaning domestic wastewater in artificial purification ecosystems due to the passage of physical, chemical and biological processes according to a typical system of cleaning and pollution control and determining the level of pollution by long-term methods.

Regarding waste disposal, the analysis of literary sources of a number of high-tech and close to natural domestic wastewater treatment technologies showed that the most promising for application on the scale of small towns, taking into account the economic and climatic conditions of Ukraine, is the technology of bioengineering ponds with a horizontal subsurface flow of wastewater and the development of structures with phytoremediation at bioengineering treatment facilities such as *Constructed Wetlands* and aerated ponds (*lagoons*) biological ponds waste stabilization ponds [18]. Bioengineering ponds in Ukraine are still often called bioengineering structures or bioplateau structures [18]. However, these structures are characterized by one significant drawback – the low efficiency of removing nitrogen compounds [19], which requires additional research. The technology of complex bio-purification facilities of the type of bioengineering ponds according to the principles of sustainable development is ecologically acceptable and economically the most promising bio-safe direction in the system of domestic wastewater treatment, water treatment, and therefore requires the use of information technologies for the careful determination and selection of the method of cleaning this industrial or domestic effluent.

A particularly important task for improving the ecology of the environment when using bioengineered ponds with microbial and phytoremediation is to increase the efficiency of removing nitrogen compounds and xenobiotics from wastewater. Based on the use of bioremediation, a technological scheme was developed for the treatment of water high-nitrogen effluents using a biocomplex by inoculation of active biomass of anammox bacteria and colonization with higher plants, which made it possible to increase the efficiency of removing pollutants and biogenic nitrogen in these ecosystems and improve the functional parameters of wastewater by intensification in bioengineering ponds with subsurface flow. The advantages of using the ANAMMOX technology are: reduction of energy costs compared to traditional nitrification - denitrification up to 60–90%; lack of need for an additional carbon source; decrease in the level of CO_2 formation up to 90%; reducing the amount of excess activated sludge; high nitrogen removal efficiency; smaller water footprint of the process [18]

The initial stage of the proposed complex bioremediation of water effluents on the basis of information technologies was the modeling of the process of biodestruction of nitrogen-containing pollutants with a bac preparation based on anammox bacteria. Based on these results, a study was conducted to investigate the content of archaea in the biofilm of developed pilot bioengineering ponds.

By modeling, designing and launching an experimental engineering installation of complex phytoremediation and anamox remediation for the conditions of wastewater in a small settlement, it was established that it is rational to use the nitrogen load as the main parameter for the design of treatment facilities on the basis. And the optimal load values for polluting substances have been determined: for nitrogen, no more than 780 mg N/(m^2·day); according to COD oxygen up to 2253 mg / (m^2 day), which is necessary for effective removal of nitrogen compounds and organic substances from wastewater [20].

Sufficient attention is paid to the study of the influence of xenobiotic pollutants or waste of natural origin on the microorganisms of water basins and on the ecology of water bodies in general, since the spread of local pollution in the water ecosystem even in the world ocean has a step-by-step trend today.

The waste of technological productions usually must be detoxified when thrown out, but it can still end up in sewage treatment plants, which are actually the main points of pollution, and also due to the emission of household waste (including synthetic and even partially biodegradable plastic) get into the water ecosystem, which negatively will affect people's well-being and health. Therefore, the study of the effect of various types of pollution on biological cleaning products at pilot plants makes it possible to simulate the process of bioremediation and, with the help of biocomputing, to predict the process of biodegradation of pollutants and the survivability of biotransformers of pollution decomposition.

The study of integrated bioremediation facilities showed the safety of using bioremediation through the complex application of microbial remediants and phytoremediates, especially from excessive nitrogen pollution based on pilot plants of bioengineering ponds [19].

During the study of complex bioremediation facilities by bioindication and biotesting of bioengineered ponds, the safety of using microbial remediants of Anamox bacteria was determined. The presence of a nitrogenous substrate in domestic sewage without prior disposal affects the growth and accumulation of biomass of pathogenic bacteria. Therefore, the use of bacterial remediation of the water environment, at least within the limits of the artificial ecosystem of treatment facilities, is promising for purification in the conditions of Anaerobic ammonium oxidation (ANAMMOX-process) to free nitrogen [21].

To solve the issues of cleaning local water ecosystems, biomonitoring of the environment is carried out using bioindication (higher plants) and biotesting of its individual components (anammox bacteria), which involves disposal, storage and processing of waste. Biocomp'ting of activity for each substance is carried out in comparison with the known physiological activity or toxicity of the corresponding substance.

When studying the composition of the microbial population by the PCR method in model and pilot ecosystems of bioengineering ponds, a number of factors were taken into account on the dynamics of the biofilm and the content of anammox bacteria. Non-specific (bacterial) as well as functional and group-specific oligonucleotide primers were used for the analysis (16S rRNA gene of eubacteria, 16S rRNA gene of anammox bacteria, 16S rRNA gene of aerobic ammonium-oxidizing bacteria, as well as functional genes: nirS gene of cytochrome cd-1 nitrite reductase, the nosZ N_2O reductase gene of denitrifying bacteria and the Arch-amoA α-subunit ammonium monooxygenase gene of ammonium-oxidizing archaea). In all studied biofilm samples, the number of genes of anammox bacteria significantly exceeded other groups of bacteria capable of transforming nitrogen compounds. In all studied biofilm samples, the number of genes of anammox bacteria significantly exceeded other groups of bacteria capable of transforming nitrogen compounds.

Based on the results of PCR-RF, conclusions were made about the importance of the role of anammox bacteria in the installations of bioengineering ponds with horizontal subsurface flow. In all studied biofilm samples, the number of genes of anammox bacteria significantly outweighed the number of genes of aerobic ammonia-oxidizing and other groups of bacteria capable of transforming nitrogen compounds. The average share of anammox bacteria in the total population of eubacteria in the biofilm on the surface of the gravel in the filter layer for pilot plants with BVR was 18.5 ± 6.0% for the entire period of the experiment. Based on the results of PCR-RF, conclusions are made about the importance of the role of anammox, which makes it possible to assess biological risks, in addition, it is possible to obtain information about microorganisms and strains, their location, as well as about the safety of personnel who need access to pathogens or toxins, or to assess threats of their improper use.

At the same time, during the biotreatment of waste water, artificial ecosystems (water treatment plants) carry out anaerobic treatment with the additional production of the energy product biogas, the production of which is harmed by the products of the oxidative decomposition of nitrogen- and sulfur-containing compounds - ammonia and hydrogen sulfide. In particular, it negatively affects the production of hydrogen sulfide (H_2S) biogas, which is formed during the decomposition of sulfur-containing substrates and mainly proteins. Control of the content of hydrogen sulfide can usually be carried out by biological (in situ microaeration) and physico-chemical methods of absorption by scrubbing with water and adsorption with activated carbon. Nitrogen-containing substrates, especially rich in proteins, can form ammonia (NH_3) as a result of decomposition, the level of which is regulated depending on the value of temperature and acidity (the pH level is high and the temperature is high, then the balance changes in the direction of ammonia). Methods of removing and controlling ammonia can be different . It is more practical to use zeolites by previously adding NaCl to it, while the experimental method of removing ammonia - the process of anaerobic oxidation of ammonium (ANAMMOX-process) needs additional research in the field of biogas production.

Also, with this cleaning, other pollutants slow down the production of biogas, including oxygen that can penetrate with an insufficiently enriched crushed substrate and harm methane bacteria, and especially high concentrations of chemical substances (antibiotics, chemotherapeutic agents, and disinfectants) can restrain the fermentation process and lead to its complete failure. stops, especially with their high concentration. A restraining effect can be given by the accumulation of organic acids, which are formed during the anaerobic decomposition of organic substances in the corresponding departments of treatment plants. With a stable process of biogas formation, the amount of organic acids (they are also called acetic acid equivalents) is normally below 2000 mg/l). If fresh or very easily decomposing substrates are fed too quickly, rapid oxidation and accumulation of acids up to the level of 16,000 mg/l can occur, as well as a negative ratio of acetic to propionic acid, which leads to a whole series of reactions, starting with the fact that high concentrations of acids restrain themselves bacteria in such a way that the pH level decreases, which causes a delay in the development of methane bacteria until the decomposition process is completely stopped. This can be countered only by a complete reduction in substrate supply. Mathematical modeling of the biorefining process and optimization of methane fermentation will help the economic benefit of the biogas production process.

Of course, in order to ensure rational surface water use and biomonitoring based on spatial and temporal changes of bioindicator components of the water ecosystem, we believe that it would also be effective to use information technologies to study the symbiosis of microflora (phyto-, bacteria-, zooplankton and benthos) and higher aquatic plants (phytocenosis) and self-restoration of phytocenoses in the next vegetation cycle, which involves the introduction of phytoremediation bioengineering ponds (BS), which can contribute to the restoration of the biological balance of the water ecosystem or the improvement of the ecological situation in the region.

The use of complex methods of thematic processing of digital images for the monitoring of the water ecosystem, in particular, the synthesis of cartographic models, the synthesis of water bodies and their technological load, the introduction of remote sensing technologies using models, methods and technologies of information support for the management and monitoring of the ecological safety of water bodies , prevention and elimination of the consequences of man-made disasters have already been proposed by scientists [22, 23].

Therefore, the combination of in silico biological activity prediction methods and in vitro microbiological testing in the context of biosafety and biosecurity allowed us to optimize the selection of basic compounds in order to increase their activity and determine the specificity of action, as well as the use of biocomputing methods made it possible to propose effective antibacterial compounds for protection against pathogenic infections, which will help protect human health. Biomonitoring can be an effective tool for pollution mapping and trend monitoring in real time and retrospective analysis. Simple and inexpensive sampling procedures allow a very large number of sites to be included in one survey. The development of modular systems and mathematical modeling in the process of bioremediation will help to identify and eliminate pollution during wastewater treatment, and waste disposal will obviously contribute to the economic benefit of the process and the biosafety of the environment.

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