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Philosophy of Antimicrobric Therapy – Guarantee to Health

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Abstract **Original Research Article**

Antimicrobial resistance is a global health threat and human development. It requires urgent efforts across a range of sectors to achieve sustainable development goals. The World Health Association (WHO) has identified 'AMR', as one of the top 10 global public health threats facing humanity. The problem generates significant economic losses. In addition to death and disability, prolonged illness leads to longer hospital stays, require more expensive medicines and create financial hardship for those affected. The aim of current study is to summarise mechanisms of resistance of microorganisms to antibiotics and especially of antibiotic resistance in Mycobacterium bovis and Mycobacterium caprae; to present new strategies for overcoming drug resistance such as new targets from the bacterial genome as bacterial riboswitches and natural derivatives with antibacterial activity and potential to modify resistance.

Keywords: Antimicrobial Resistance, Antibiotic Resistance, Antibacterial Targets, Bacterial Genome, Mechanisms of Resistance, Tuberculosis.

INTRODUCTION

I. Antibiotic Resistance

To better understand the problem, it is important to clarify the difference between antibiotic [1] and antimicrobial resistance [2]. Antibiotic resistance is related to the development of mechanisms in microorganisms by which they overcome the effects of antibiotics [1], while antimicrobial resistance (Fig. 1.) is a broader concept that refers to resistance to various drugs – antiviral (with the obligatory clarification that viruses are not actually microbes but as a significant pathogen for humans they are included in this category), antifungal, antibacterial and antiparasitic [2].

Antibiotic resistance and the inability of traditional medicines to affect infections caused by bacteria is leading to a huge number of deaths and is a serious problem associated with social, moral and economic danger. Antibiotic resistance, declared by the World Health Organisation (WHO) as one of the ten greatest global health threats facing humanity, is a critical global problem affecting people around the world. This is example of the opportunity for biotechnology, bioinformatics, genetic engineering and Microbiology to be in sync to discover new antibacterial targets, exploit new technologies, molecular mechanisms and innovative antibacterial agents to overcome antibiotic resistance [3]. On Fig. 2. are presented the possibilities of regulatory authorities to support the accelerated approval of antibiotics.

As a result the ineffectiveness of antibiotic therapies, treatment in home and hospital settings are prolonged, drug costs are rising and bacteria are increasingly antibiotic insensitivity. Approximately 1.27 million deaths have resulted from infections caused by resistant and multidrug-resistant bacteria whose treatment has been unsuccessful [4]. The growing problem of the ever-increasing antibiotic resistance in bacteria infects man. It is very important to focused on the discovery of novel targets from the bacterial genome of resistant and multidrug-resistant bacteria such as Escherichia coli, Listeria monocytogenes, Staphylococcus aureus and others [5], as well as the development of new therapeutic drugs with bacteriostatic or bactericidal effects and the analysis of the possibility of future resistantion to them [6].

Fig. 1: Antimicrobial resistance

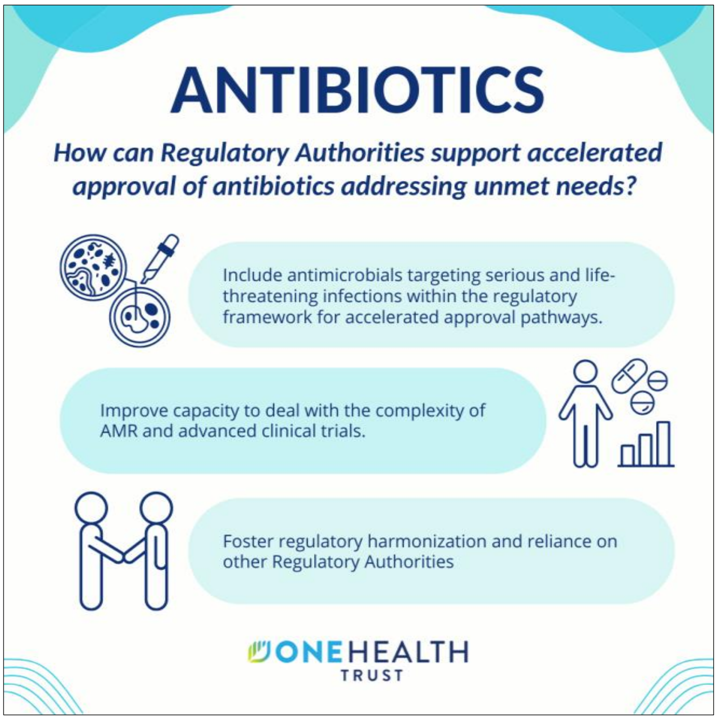

Fig. 2: Regulatory Authorities support accelerated approval of antibiotics

Fig. 3. presents antimicrobial resistance and resistance of antibiotic.

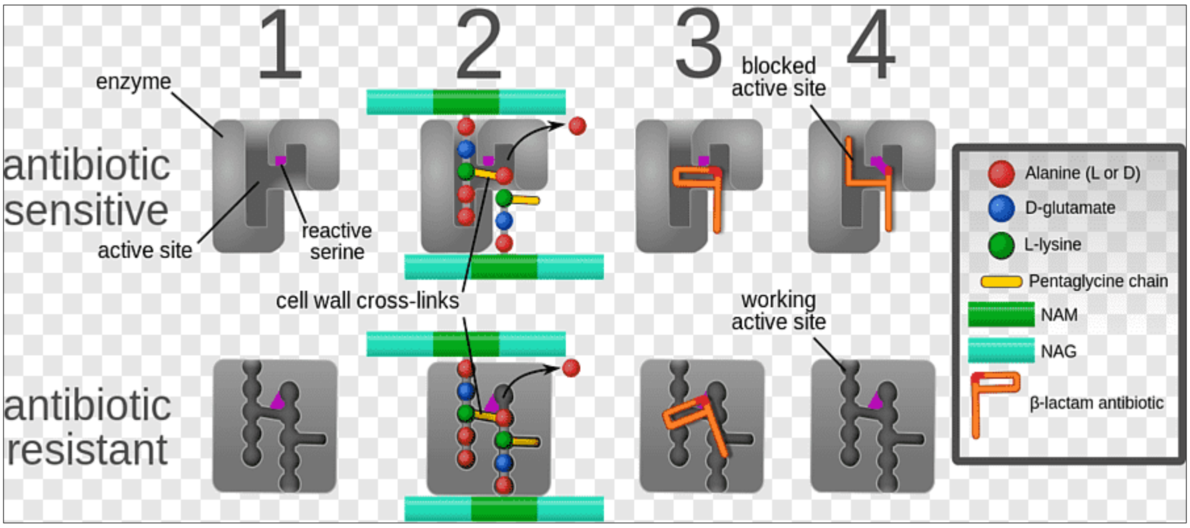

Fig. 3: 1. β-lactam antibiotic 2. Antimicrobial resistance 3. Antibiotics Beta-lactam, 4. Resistance of antibiotic

Antibiotic resistance is a serious public problem that directly affects the population of the Earth. In 2019, the World Health Organization (WHO) declared antimicrobial resistance as one of the ten greatest public health threats facing humanity [7].

II. Antimicrobial Resistance

Antimicrobial resistance and its spread is a global threat [8]. Global projections show that if no measures are taken to overcome antibiotic resistance, by 2050, the number of victims of reduced sensitivity to antibiotics will reach 10 million people per year m [9].

Today, statistics indicate that antimicrobial is responsible for the death of 1.27 million people worldwide and is linked to the death of at least another 5 million people. According to recent data, trends in the number of infections and associated deaths are significantly increasing for almost all antibiotic-resistant bacteria, especially in healthcare settings [8]. In July 2022, the Commission and the European Union (EU) countries identified antibiotic resistance as one of the three biggest health threats and a significant priority [10].

Antibiotic resistance occurs in bacteria as a defense mechanism by which they become insensitive to antibiotic agents with which they have been successfully treated until now [11].

It was observed as a protective mechanism immediately after discovering the first antibiotics and their mass application. The discovery of antibiotics is one of the greatest discoveries for medicine and humanity because, thanks to them, many infectious diseases that were deadly to humans they are now being treated successfully. In the 1940s, Alexander Fleming predicted that excessive use of penicillin could lead to the development of resistance, so he recommended its rational use. In the early years after the war, access to and use of antibiotics increased, and today, they are available in a wide variety of forms - injectables such as liquids and suspensions, liquid for instillation in the eyes or including a system, cream or spray for surface treatment, pills and capsules for oral use. Their low production cost, wide availability, initial effectiveness, and absence of an antibiogram for each patient are the main factors leading to their wide application [11].

Everything listed here confirms the relevance of the problem. It shows us the need for new studies that aim to develop or discover new antibacterial preparations - effective, not leading to the development of antibiotic resistance, and applicable *in vivo* in humans or animals, as well as new targets of the bacterial genome that have not been tested to date [11].

III. The Current State of the Research on the Problem Area

To date, we scientists are developing new strategies to search for antibacterial targets different from those used to date to avoid the emergence of antibiotic resistance [12]. New therapeutic preparations are being created, most of which reach a stage where they are effective in the short term and quickly, after the start of their application, begin not to affect the bacteria they are targeting. Bacteria are highly variable organisms that quickly adapt to different environmental conditions. Some bacteria enzymatically degrade substances; others use alternative biochemical pathways to synthesize important metabolites [13].

One of the proven effective targets in the bacterial cell is ribonicleinic acid (RNA) [13], a large percentage of antibiotics developed and under development target ribosomal RNAs. One of our areas of work is the analysis of bacterial riboswitches. Riboswitches are functional domains often found in the untranslated regions of mRNAs in many bacteria, fungi, and some plant species, and they are responsible for controlling gene expression directly by binding metabolites [14]. They are not found in the human genome; this is their first major advantage [15].

Riboswitches control the biosynthesis of certain vitamin precursors such as riboflavin, thiamine, and cobalamin [16]. They control the synthesis of essential amino acids, such as methionine and lysine, and nucleotides, including adenine and guanine [17]. Bacterial riboswitches regulate gene expression through four different regulatory mechanisms [18]. Three are cis-acting regulatory mechanisms: translation prevention, transcription termination, and mRNA destabilization. The fourth mechanism for gene regulation using riboswitches is pathway-acting [19, 20].

For this purpose, specific ASOs were designed, which are highly sensitively recognized by riboswitches and lead to the regulation of gene expression [21, 22]. In 2022, for the first time, a description of the design of ASOs targeting riboswitches of the FMN class of riboswitches in the bacterial species Staphylococcus aureus, Listeria monocytogenes, and Escherichia coli was officially published [23].

Two glucosamine biosynthetic pathways are observed in Staphylococcus aureus, which is under the control of separate glucosamine-6-phosphate riboswitches. To influence bacterial growth, we applied a combination therapy of two ACO agents designed to specifically recognize and bind the individual glmS riboswitches - core and nagA. We assessed that administered in combination, ASOs completely blocked the synthesis of glucosamine-6-phosphate and inhibited the bacterial growth of S. aureus. It has been found that the first ASO that targets the riboswitch regulating the major pathway of glucosamine synthesis inhibited 80% of bacterial growth at a dose of 5 μg/ml. This means that at a given concentration of the antibacterial agent, the alternative biosynthetic pathways fail to compensate for the amount obtained from the primary pathway.

IV. Mechanisms of Resistance

Today, two main mechanisms are known for inhibiting mRNAs by antisense oligonucleotide technology. The first involves RNA degradation by RNase H or RNase P after ACO hybridization to the target mRNA. In this case, first- and second-generation ACOs are usually used, which can induce ACO-directed enzymatic degradation of RNA. In ASO's second mechanism of action, the target mRNA is not degraded, but its translation is blocked by hybridization with third-generation ASO. In this case, ASO usually targets a region of the mRNA that contains a start codon, leading to the prevention of translation [24].

The emergence of resistance in a number of pathogenic bacteria against the administered drugs is a serious challenge of our time, therefore the development of new antibacterial agents to reduce the treatment time, to affect the resistant strains and to increase the effect of the administered treatment is relevant and significant. Of particular interest is the search for new pharmacological agents suitable for antitumour and antibacterial therapies. The use of natural products and their synthetic derivatives appears to be a serious alternative and this is where the tasks in this project are directed. An interesting idea and expectation of the effect of the new natural molecules and derivatives is presented, and it is based on a growing interest in drug structures containing the transition element iron in the form of ferocen.

V. Some Natural Derivatives with Potential Antibacterial Abd Anticancer Activity

Treatment of infections in recent years continues to be a serious challenge, despite advances in clinical microbiology and infectious diseases. The reason is the emergence of resistance in a number of pathogenic bacteria against drugs. To control this global problem, there is an urgent need to develop new antibacterial agents to reduce the time to treatment, to act on resistant strains and enhance the effect of treatment.

Successful approach for the discovery of novel pharmacological agents suitable for antibacterial and antitumor therapies is the use of natural products and their synthetic derivatives [25]. Examples of such biologically active structures are triterpenic acids, which demonstrate significant biological activity with broad spectrum of action. Triterpenic acids are valuable molecules that can be modified by the synthesis of derivatives containing suitable active groups that modulate various regulatory pathways in the cell, thereby potentially enhancing their pharmacological effectiveness against both oncological and infectious diseases [26].

Thus potentially can be improved their pharmacological effectiveness against both oncological and infectious diseases. Triterpenic acids, in particular olenol and boswellic acids, are suitable pharmacophore groups for the design of new drug candidates, especially in the occasional, when ferrocene is included as a second functional group. Ferrocene is a structure with high biological potential that can enhance antibacterial and antitumor activity of the hybrid structures synthesised with triterpenic acids, [26]. These new nature-inspired hybrid structures offer opportunities to overcome drug resistance and to expand the therapeutic capabilities of modern drugs.

The objectives of such studies include: fractionation of boswellia extract to isolation of pure natural substances, characterization of the compounds by spectral methods; synthesis of ferrocene-containing derivatives and their structural characterization. In addition, theoretical calculations (Density Functional Theory (DFT) and TDDFT (Time-Dependent DFT)) are important to better understand the structural and electronic properties of the investigated compounds, which will support the design and prediction of their biological activity.

Advances in medicine and biology over the past decade has led to the development of new and innovative anti-tumor therapies based on molecular mechanisms, immunotherapy and targeted therapies. Interest is shifting from agents to the application of therapies with specific analogues, methods and approaches tailored to the biology of the cancer and the pathophysiological state of the patient. The main reason for this is the development of new target molecules and the establishment of interactions that determine disease pathogenesis and progression [27].

The emergence of resistant and multidrug-resistant tumours requires the development and synthesis of more effective chemotherapeutic agents. Such complex agents, which have in the structure several active groups, can modulate different regulatory pathways in the cell, which leading to their higher efficacy than those affecting only one cellular process. The search for such structures has been a challenge that has guided scientists in the search for alternative pathways for their design and synthesis [27].

VI. State of Research on the Problem

Triterpenes are a large group of secondary metabolites represented by over 2000 natural substances with molecular formula $C_{30}H_{48}$. In plants, their biosynthesis starts from cyclization of squalene or from related acyclic precursors containing 30 carbons atoms. Natural triterpenic acids and their derivatives, part of the larger group of triterpenes, are widely distributed in higher plants and cause interest due to their structural diversity and their wide range of bioactivity. Particular, structurally diverse triterpenic acids and derivatives have been reported in the literature that possess high potential as anticancer agents. For example, triterpenic acids are ursolic and oleanolic acid, betulinic acid, celastrol and pristimerin.

It has been reported that triterpenes can exert antimicrobial activity and can play role as resistance modifying agents against Staphylococcus aureus [28]. This is an example how plant compounds can help for overcoming of antibiotic resistance in bacteria.

VI. Determinants of Antibiotic Resistance in Mycobacterium Bovis (M. bovis) and M. caprae and tracing of Interspecies Transmission

Tuberculosis is an infectious disease of societal importance that is leading ininfectious disease mortality of all time. According to the WHO, in 2022 in worldwide, 10.6 million people have contracted tuberculosis and 1.3 million deaths [29]. In addition to the human population, tuberculosis also affects other vertebrate species - domestic and wild animals, forming reservoirs of endemic spread.

The widespread and inappropriate use of antibiotics in animal and health care favours the emergence and spread of mutations in bacteria found in humans, animals, water, soil, plants, food products and can spread from one source to another. As a result, the incidence of infections, caused by antibiotic-resistant bacteria is increasing every year as in humans, Resistance in MTBC is particularly problematic because the spectrum of agents with which it can be successfully treated is extremely narrow. Therapeutic regimen for patients with tuberculosis includes the following anti-TB agents drugs: rifampicin, isoniazid, ethambutol, pyrazinamide. Of those adapted to animals species, M. bovis most commonly causes disease in humans, with clinical manifestation is identical to that of M. tuberculosis sensu stricto, but the incidence of extrapulmonary localization is higher.

Treatment of M. bovis infection in man is with rifampicin, isoniazid and ethambutol; duration is 9-12 months, a pyrazinamide is dropped from the treatment regimen due to innate resistance of M. bovis. Even properly assigned on the basis of species specificity, treatment of M. bovis infection in humans is with unsatisfactory results and with high mortality rates, which is an indisputable motive for in-depth studies on adapted animal representatives of MtbV and human infections.

A meta-analysis of published cases between 2009 and 2019 shows that, on average, worldwide M. bovis causes 9.7% of tuberculosis cases in humans, with individual countries. The percentage varies between 0.4% and 76.7%. Only reported cases of tuberculosis in humans caused by M. bovis or M. caprae in the EU in 2022 were 130, of which 16 resulted in fatal. Compared to the previous year, reported cases increased by 13.2%. The incidence of M. bovis/M. caprae infection in humans in the EU has also been calculated: for countries, officially eliminated bovine tuberculosis in EVW is 0.03 per 100,000 population, and in Member States with outbreaks of bovine tuberculosis is 0.04 per 100 000 population. People with TB disease are compulsorily reported with individual data, but what proportion of them contracted M. bovis or M. caprae is unknown - not every country makes a species-specific identification of the tuberculosis causative agent in its routine diagnosis, so the real picture cannot be presented [29]. More genomic analysis of diversity, biogeography, and drug resistance in Mycobacterium bovis are needed [30].

Resistance in MTBC has been addressed at European level in the direction of tuberculosis prevention and infection control in humans by the European Centre for Disease Prevention and Control, which coordinates scientists and laboratory professionals in the EU/EEA. The EU monitoring and information collection system is based on Directive 2003/99/EC1. All this proves the correct choice and approach of the project authors and their choice of objective. The expected results related to new knowledge are related to finding out exactly which species are involved in human pathology in the territory of the country - the first study of its kind with this focus in our territory. It is expected to find M. bovis which causes tuberculosis in humans, and the proportion in those affected would be an indicator of the control of tuberculosis.

CONCLUSION

The increased antimicrobial resistancre is an evidence for ineffectiveness of antibiotic therapy and this shows the current aim of scientists for investigastion of new antibacterial drugs with decreased possibility for the development of resistance to them. Other strategies for overcoming of resistance is the need for new studies for discover of new targets of the bacterial genome as riboswitches. Other trend can be investigation of natural derivatives with antibacterial activity and potential to modify bacterial resistance.

Abbreviations

AMR Antimicrobial Resistanc
DFT Density Functional Theory
EU European Union
RNA ribonicleinic acid
TDDFT Time-Dependent Density Functional Theory
WHO World Health Association

Remark: The figures in this work are borrowed from the sites:
https://my.clevelandclinic.org/health/articles/21655-antibiotic-resistance
https://en.wikipedia.org/wiki/Electrical_resistance_and_conductance
https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance
https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance

ADDITIONAL INFORMATION

Conflict of Interest

The authors have declared that no competing interests exist.

Ethical Statements

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study

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Author Contributions: All authors have contributed equally.

Data Availability

All of the data that support the findings of this study are available in the main text or Supplementary Information.

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