*https://doi.org/10.31925/farmacia.2026.1.4* **REVIEW**

# APPLICATION OF ARTIFICIAL INTELLIGENCE IN SEARCHING FOR NEW APPROACHES TO FIGHT ANTIMICROBIAL RESISTANCE

SILVIYA GEORGIEVA MIHAYLOVA [1], MOMCHIL KONSTANTINOV LAMBEV [1]*, PLAMEN STEFKOV BEKYAROV [1,2], DIMANA DIMITROVA GEORGIEVA [1], MARIYA GAVRAILOVA DANGOVA [1], ANTOANETA ZDRAVKOVA TSVETKOVA [1]

[1]*Medical college, Medical University of Varna, Varna, Bulgaria*
[2]*Specialized Hospital of Obstetrics and Gynecology for Active Treatment "Prof. Dr. D. Stamatov", Varna, Bulgaria*

**corresponding author: momchil.lambev@mu-varna.bg*

*Manuscript received: October 2025*

**Abstract**

Artificial intelligence (AI) has emerged as a promising tool to support efforts addressing antimicrobial resistance (AMR) by improving diagnostic accuracy, optimizing antimicrobial therapy, and accelerating drug discovery. This review systematically examines studies published between 2013 and 2023 that apply AI-based approaches to combat AMR, with emphasis on clinical decision support and the discovery of new antimicrobial agents, including antimicrobial peptides. A structured literature search was conducted in PubMed, Scopus, and Web of Science following PRISMA guidelines, using predefined search strategies and eligibility criteria. The findings indicate that machine learning and deep learning methods can enhance pathogen identification, support rational antibiotic use, identify synergistic drug combinations, and facilitate the *in silico* design of novel antimicrobial compounds. In addition, AI-driven models show promising accuracy in predicting antimicrobial peptide activity. The translation of AI-based models into clinical practice is limited by heterogeneous and biased datasets, restricted model interpretability, limited generalisability, and the absence of robust prospective clinical validation studies. Overall, AI offers valuable supportive tools in the fight against AMR; however, further validation and integration into clinical practice are still required.

**Rezumat**

Inteligența artificială (IA) a devenit un instrument important pentru eforturile de combatere a rezistenței antimicrobiene (RAM), prin creșterea acurateței diagnostice, optimizarea terapiei antimicrobiene și accelerarea proceselor de descoperire de noi medicamente. Acest articol analizează sistematic studiile publicate în perioada 2013–2023 care au aplicat abordări bazate pe IA pentru limitarea RAM, cu accent pe sistemele de suport decizional clinic și pe identificarea de noi agenți antimicrobieni. A fost realizată o căutare bibliografică structurată în bazele de date PubMed, Scopus și Web of Science, în conformitate cu ghidul PRISMA, utilizând strategii de căutare și criterii de eligibilitate predefinite. Rezultatele sugerează că metodele bazate pe *machine learning* și *deep learning* pot îmbunătăți identificarea patogenilor, susține utilizarea rațională a antibioticelor, evidența combinații medicamentoase sinergice și facilita proiectarea *in silico* a unor noi compuși antimicrobieni. De asemenea, modelele dezvoltate prin IA demonstrează performanțe promițătoare în predicția activității peptidelor antimicrobiene. Implementarea clinică a modelelor bazate pe IA rămâne însă limitată de eterogenitatea seturilor de date, interpretabilitatea redusă a modelelor, generalizabilitatea limitată și absența unor studii prospective robuste de validare clinică. În concluzie, IA oferă instrumente valoroase de suport în combaterea RAM; cu toate acestea, sunt necesare validări suplimentare și o integrare atentă în practica clinică.

**Keywords**: artificial intelligence, AMR, new antibiotics, AMPs

## Introduction

Products of natural origin demonstrate higher affinity to bind to biological receptors. This fact results in scientists creating new drug molecules whose structure is close to that of the natural molecules. In the period 1980 - 2010, more than half of the new medicinal products were of natural origin in a different form: unchanged (5%), analogues (28%), or containing natural pharmacophores (35%) (1). However, pharmaceutical companies avoid the production of new drugs of natural origin because the process is lengthy, complex, and error-prone (2, 3), and the molecules possess limiting characteristics such as a high degree of stereochemistry, rotatable bonds, and fused rings (4, 5). In order to overcome some of these limitations' scientists use the capabilities of artificial intelligence.

Artificial intelligence (AI) refers to the ability of computers to receive, process, and recognize large volumes of complex data. One of the widely used types of AI is machine learning (ML) which uses

mathematical and statistical calculations set by a human to solve a particular problem (6, 7).

The "Golden Era" of antibiotics has been followed by increasing of AMR (8). AI has emerged as a promising tool to support strategies addressing antimicrobial resistance (AMR); however, its impact is currently limited to specific applications and remains largely dependent on data availability and clinical validation (9, 10). It is applied to study resistant bacteria (11-13), supporting the rational antibiotic use by collecting and providing clinical data necessary for more accurate therapeutic decisions (14). It can also provide information for choosing an appropriate synergistic drug combination (15). AI can take part in the creation of new antibiotics (16) and can perform simple and repeatable actions during the process, thus allowing scientists to focus on researching the scientific problem (17).

The development of supercomputers, the opportunities for multi-data storage, the existence of comprehensive databases, and parallel computing accelerate the development of computer-aided drug design (CADD). Computational and *in silico* methods typically use the provided data to investigate the function of molecules, aiming at the future design of new drugs. ML accelerates the discovery of the target and the antimicrobial agent, as well as the preclinical and clinical development. ML models can identify the mechanisms of action of antimicrobial agents with unknown functions, cytotoxicity, and resistance mechanisms (18). CADD allows researchers to avoid "wrong" trials and this way it saves time, money and effort. Approaches that use machine learning allow rapid identification of the physiological processes that are involved in the drug-target interaction. AI increases the opportunities for success in the later stages of the drug development by predicting the course of its absorption, distribution, metabolism, excretion and toxicity. Another advantage of the *de novo* drug design is that no model molecule is used to create new drugs (19, 20).

The presented review aims to systematically examine studies for 10 years period applying AI to fight AMR, with emphasis on clinical decision support and antimicrobial drug discovery.

## Materials and Methods

To achieve the scientific research objective, we used the documentary method. To conduct our research, we analysed scientific papers focusing on the topics of antimicrobial resistance, artificial intelligence, and design of new antibiotics from natural products. A structured literature search was performed in the electronic databases PubMed, Scopus, and Web of Science. The search covered a period of 10 years (2013 - 2023). The final search was conducted on 05$^{th}$ October 2024. Two separate search strategies were applied in order to address different aspects of the research topic, which are presented in Figures 1 and 2.

The following search strings were used: (i) Search strategy 1 - AI in diagnosis and therapy of antimicrobial resistance with keywords: "artificial intelligence" AND "antimicrobial resistance" AND "diagnosis" AND "therapy"; (ii) Search strategy 2 - AI-based discovery of antimicrobial peptides with keywords: "artificial intelligence" AND "antimicrobial resistance" AND "peptides".

Studies were included if they met all of the following criteria: published between 2013 and 2023, written in English, available as open-access full-text articles, classified as original articles, belonging to the fields of medicine, pharmacology, toxicology, pharmaceutics, chemistry, or chemical engineering.

The exclusion criteria were: review articles, editorials, conference abstracts, or opinion papers, articles not related to the topic of antimicrobial resistance and artificial intelligence, studies outside the defined scientific fields, duplicate records identified across databases, articles without accessible full text.

All records retrieved from the databases were exported and screened. Duplicate records were removed prior to screening. Titles and abstracts were initially screened for relevance. Subsequently, full-text articles were analysed for eligibility according to the predefined inclusion and exclusion criteria.

The study selection process is illustrated using PRISMA flow diagrams in Figures 1 and 2, showing the number of records identified, screened, excluded, and finally included in the review.

This review has several limitations. In the early detection process, we used only three of the biggest scientific databases, and the inclusion was restricted to English-language and open-access publications. Additionally, the selection of keywords may have limited the retrieval of potentially relevant studies. Therefore, some relevant publications may not have been captured.

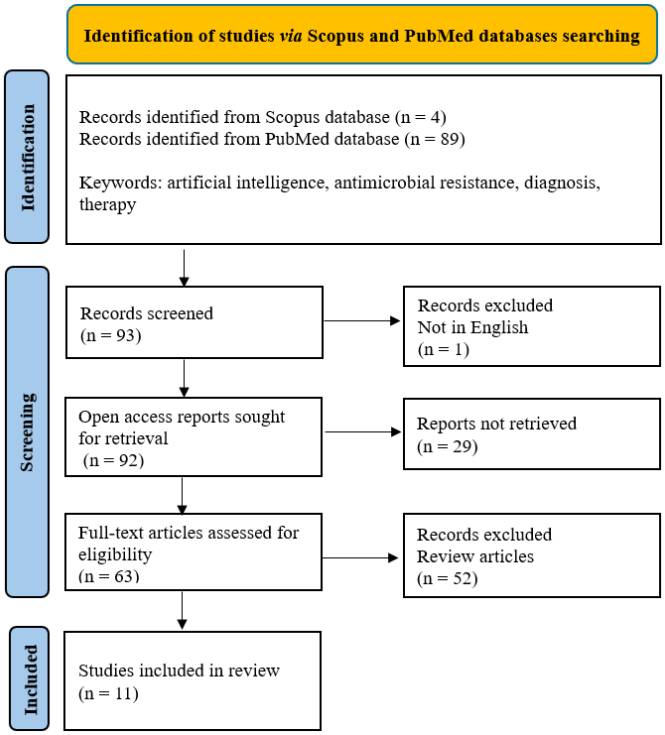


**Figure 1.**
Overview of the search process (artificial intelligence, antimicrobial resistance, diagnosis, therapy)

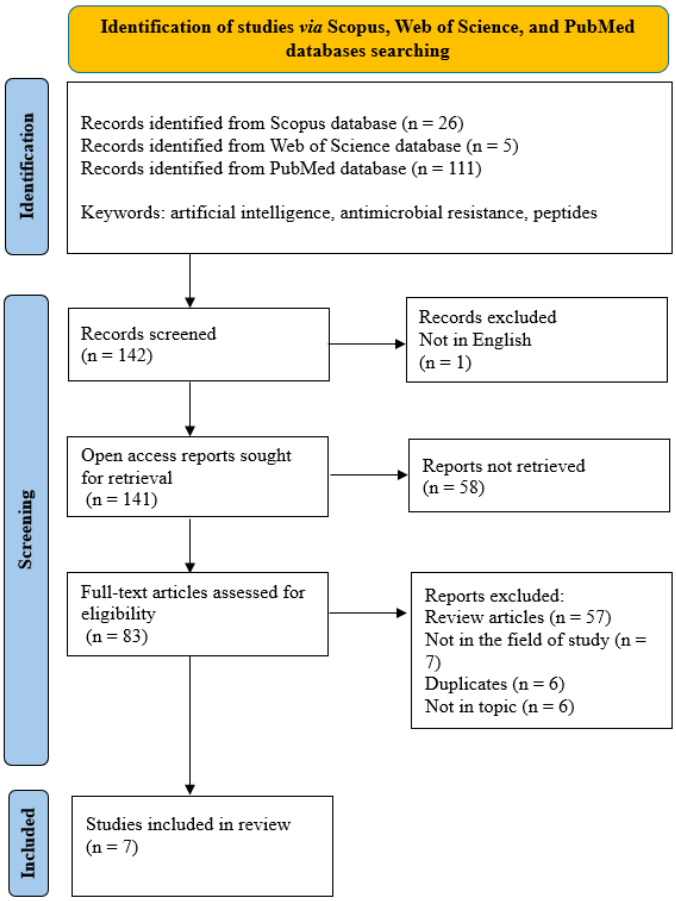


**Figure 2.**
Overview of the search process (artificial intelligence, antimicrobial resistance, peptides)

## Results and Discussion

*Application of AI in diagnosis and selection of appropriate therapy*

The main role in the fight against AMR is played by the accurate diagnosis of the disease. One of the factors to achieve this goal is the opportunity to recognize whether the disease is infectious or non-infectious in its nature. In addition, the main obstacles related to the rational use of antimicrobial agents must be overcome, such as the selection of an appropriate antibiotic for the specific causative agent and its route of administration, as well as the prescription of the optimal dose and dose regimen (21).

*AI as a diagnostic tool.* Diarrhoea is one of the leading causes of morbidity and mortality in children in low- and middle-income countries. The use of ML methods *(e.g.* random forest, neural networks, and support vector machine) meets the need for approaches that can support the decision-making process related to the treatment of diarrhoea. They can accurately predict the aetiology of diarrhoea, as well as reduce the reliance on laboratory tests for diagnosis.

In order to select the appropriate clinical diagnostic predictors, the data of 3366 cases of diarrhoea, in 7 countries, included in the Global Enteric Multicentre Study (GEMS) (22) were used. From these, the five most important etiological factors that can help in recognizing the cause of diarrhoea are highlighted: age, season, height-for-age-z-score (HAZ), bloody diarrhoea, and vomiting. The proposed model demonstrates a sensitivity of 0.59, when recognizing whether the disease is of viral or other origin. Vomiting, higher HAZ, and a dry or cold season were found to indicate that the causative agent was a virus, while older age and the presence of bloody diarrhoea were evidence that the disease was of a different origin. A disadvantage of the model is that when a non-viral causative agent is established, it cannot be distinguished whether it is bacterial or parasitic, which requires a different therapeutic approach (23). The research team continued refining its model to improve its performance. As a result, in 2021, Brintz *et al*. modified their model and conducted an evaluation concerning the appropriate prescription of antibiotics. New models were developed and further tested using varying levels of sensitivity and specificity: (1) 0.7 sensitivity and 0.95 specificity, (2) 0.9 sensitivity and 0.95 specificity, and (3) 0.7 sensitivity and 0.7 specificity. These modifications led to promising outcomes, reducing inappropriate antibiotic prescription or use in cases of viral diarrhoea by 53% (model without additional testing methods), 61% (model with additional testing 3), 80% (model with additional testing 1), and 93% (model with additional testing 2), respectively (24).

*AI as a tool for the choice of an appropriate antibiotic dosage regimen.* The discovery of penicillin in 1928 dramatically changed the health and well-being of humans and animals (25). The subsequent discovery of other antibiotics further increased survival rates, especially after their use in surgery and during cancer chemotherapy. However, an increased bacterial resistance is currently observed, which WHO defines as one of the major health problems of the 21$^{st}$ century (26). One of the main reasons for its appearance is the lack of new drugs to treat bacterial infections, as well as the excessive use and misuse of antibiotics. Therefore, finding optimal dose treatment regimens is critical to ensure the continuous effectiveness of antibiotics. As a new possibility to address this problem, Paterson *et al*. create a genetic algorithm (GA) that improves treatment regimens. It can identify appropriate therapeutic regimens and minimize the amount of antibiotics used while maximizing bacterial eradication, but it is still not included in clinical practice (27).

AI has the potential to help clinicians make decisions for combining antimicrobial agents. Clinical practice confirms increased effectiveness, reduction of side effects (28), and resistance control of the antibiotic combinations. However, it is difficult to find the optimal drug combination from a large number of possible ones (29) due to many factors, for example, drug toxicity, pharmacokinetics, pharmacodynamics (30), etc. For this reason, AI can be efficiently used (31). For example, Smith *et al*. developed a genetic algorithm (GA) that can be used in therapy to optimize the treatment of CRAB (Carbapenem-Resistant Acinetobacter baumannii) infections by selecting appropriate therapeutic concentrations of a combination of polymyxin B and meropenem (32).

Another example of an AI-based platform designed to identify suitable drug combinations for treating vesicular stomatitis virus (VSV) infection is Project IDentif.AI. The platform was developed to rapidly identify effective therapeutic combinations for treating the mentioned infection. The concept emerged during the COVID-19 pandemic, a period marked by using various drug combinations (some repurposed from their original indications) to treat the disease.

As a result, the team behind Project IDentif.AI included 12 drug candidates in the platform, selected based on multiple factors, primarily their prior use in treating COVID-19 *(e.g.*, amantadine, dexamethasone, azithromycin, chloroquine diphosphate, among others). The platform operates through a four-dimensional framework that integrates input parameters such as drug identity and dosage with output parameters such as efficacy and safety, aiming to identify synergistic therapeutic combinations.

This approach avoids a trial-and-error strategy and minimizes delays in selecting effective treatment regimens. At the time of the publication by Abdulla *et al.*, the platform had not yet been tested in a clinical setting. Furthermore, the developers recommend that, in clinical practice, the selection of drugs eligible for combination should be carried out by a qualified medical specialist (33).

*Drug repurposing.* By using Artificial neural network (ANN), it was found that Halicin®, structurally similar to metronidazole and originally studied as an antidiabetic agent, *in vitro* exhibits antibacterial activity against various harmful bacterial strains, including multidrug-resistant bacteria (34). Stokes *et al*. combined *in silico* predictions and empirical investigation to discover a new broad-spectrum antibiotic, Halicin®, which is a potent inhibitor of *E. coli* growth. Approximately 2300 compounds were screened to predict the growth inhibition of *E. coli,* and the resulting data were used to train a deep neural network (DNN) for predicting antimicrobial activity from the chemical molecule. In a subsequent study, the inhibitory activity of the molecule against both *C. difficile* and *A. baumannii* was evaluated. The promising bactericidal activity of Halicin® led to its evaluation in murine models. Initially, an *in vitro* study was conducted on an *A. baumannii* 288 strain, which exhibited resistance to all currently used antibiotics for treating infections caused by this pathogen. The observed promising effect (MIC = 1 μg/mL) prompted researchers to proceed with *in vivo* testing.

An experiment was carried out using mice with wounds infected by *A. baumannii*, which were divided into a treatment group and a control group. The treatment group received a 0.5% cream formulation containing Halicin®, applied at 4, 8, 12, 20, and 24 hours. After the final application, it was found that 5 out of 6 mice treated with Halicin® had bacterial loads of less than $10^3$ CFU/g, while one mouse exhibited approximately $10^5$ CFU/g. These positive results encouraged the research team to investigate the antibacterial activity of Halicin® against *C. difficile*.

Again, the evaluation began with an *in vitro* study, in which the MIC was determined to be 0.5 μg/mL. The *in vivo* efficacy of Halicin® was compared to that of metronidazole, a first-line treatment for infections caused by *C. difficile*. Over a period of five days, faecal samples were collected every 24 hours to measure the bacterial content. By the end of the study, Halicin® had eradicated *C. difficile* in 3 out of 4 mice within 72 hours. By 96 hours, no detectable levels of *C. difficile* were found in any of the tested animals (35). The demonstrated potential of the application in experimental studies indicates that its inclusion in future clinical trials and monitoring of the antimicrobial effect in humans is possible.

*Application of AI in search of peptides with antimicrobial activity*

Antimicrobial peptides (AMPs) are considered a potential alternative to conventional antibiotics (36). They are a key component of the innate immunity of organisms and have a wide range of activity against various pathogens - viruses, bacteria, parasites, and fungi (31, 37, 38). The use of AI algorithms enables the creation of AMPs of promising antimicrobial activity. Table I summarizes the data on the models included in the literature review, based on the developed PRISMA diagram (Figure 2). The table contains the algorithms used to construct the models, their accuracy, and the MIC values against different strains of *S. aureus*, *P. aeruginosa*, and *E. coli*. These values correspond to the peptides with the highest antimicrobial activity, which were synthesized based on their predicted efficacy using the newly developed AI models.

**Table I**

Type of AI algorithm and accuracy (ACC) of models included in the review

| | | | | MIC (μg/ml) | | | | |
|---|---|---|---|---|---|---|---|---|
| **AI Type** | **Evaluated Model** | **Type of AI algorithm** | **Peptides** | ***S. aureus* (ATCC 25923)** | ***P. aeruginosa* (PAO1)** | ***E. coli* (ATCC 25922)** | **ACC** | **Ref.** |
| **Machine Learning** | ML model | Machine Learning | DP2 | 32 | 32 | 32 | ND | (39) |
| | | | DP3 | 8 | 32 | 8 | | |
| | | | DP4 | 32 | 64 | 64 | | |
| | | | DP5 | 16 | 32 | 16 | | |
| | | | DP6 | 32 | 128 | 32 | | |
| | | | DP7 | 16 | 16 | 16 | | |
| | | | DP8 | 16 | 16 | 16 | | |
| | | | DP9 | 32 | 64 | 32 | | |
| | | | DP10 | 64 | 64 | 32 | | |
| | | | DP11 | 16 | 32 | 16 | | |
| | | Control | HH2 | 64 | 128 | 32 | N/A | |
| | | | Bac2A | 64 | 64 | 64 | | |
| | | | Indolicidin | 16 | 64 | 32 | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Deep Learning** | **Evaluated Model** | **Type of AI algorithm** | **Peptides** | ***S. aureus* (ATCC 25923)** | ***P. aeruginosa* (H103)** | ***E. coli* (ESBL)** | **ACC** | **Ref.** |
| | DL (ANN) model | ANN | 8 | 5.9 | 5.9 | 12 | 0.94 | (40) |
| | | | 9 | 2.9 | 2.9 | 5.7 | | |
| | Deep-AmPEP30 | CNN | | ND | | | 0.77 | (41) |
| | DL (RNN) model | RNN | | ND | | | 0.814 – 0.957 | (42) |
| | **Evaluated Model** | **Type of AI algorithm** | **Peptides** | ***S. aureus* (ATCC 6538P)** | ***P. aeruginosa* (ATCC 10148)** | ***E. coli* (ATCC 25922)** | **ACC** | **Ref.** |
| | AMPlify | RNN | RaCa-1 | NI | NI | 10 - 20 | 0.937 | (43) |
| | | | RaCa-2 | 1 - 2 | 25 - 49 | 2 - 6 | | |
| | | | RaCa-3 | ≥ 78 | 20 ≥ 78 | 2 - 5 | | |
| | | | RaCa-7 | ≥ 88 | NI | 6 - 44 | | |
| | | Control | LL-37 | NI | 7 ≥ 57 | 2 - 4 | N/A | |
| | | | Tp0751 | NI | NI | NI | | |
| | **Evaluated Model** | **Type of AI algorithm** | **Peptides** | ***S. aureus* (ATCC 29737)** | ***P. aeruginosa* (ATCC 9027)** | ***E. coli* (ATC 25922)** | **ACC** | **Ref.** |
| | CLaSS | RNN | YI12 | 7.8 | 125 | 31.25 | 0.668 – 0.943 | (44) |
| | | | FK13 | 15.6 | 62.5 | 31.25 | | |

ND – No data available; N/A – Not applicable; NI – No inhibition observed *in vitro*

*Methods based on machine learning.* Wu *et al*. created an ML model that estimates how each of the amino acids in a peptide contributes to its antimicrobial activity. To verify the effectiveness of the created method, Wu's team conducted MIC tests with some of the obtained AMPs against different reference strains: *P. aeruginosa* (PAO1), *S. aureus* (ATCC 25923 and ATCC 33591), *E. coli* (ATCC 25922), and *S. enterica serovar Typhi*. As a control peptide for the *in vitro* and *in vivo* activity studies, a peptide was used that also served as a model for the synthesis of the new AMP, in which structural changes were undertaken to increase its activity. From the newly obtained peptides, the 10 predicted to have the highest activity were selected from 424 12-mer peptides and tested against *S. aureus* (25923), *E. coli*, *P. aeruginosa,* and *S. enterica serovar Typhi*. The majority of peptides demonstrated good antimicrobial activity, even at an MIC of 16 µg/ml. Then, the four peptides that showed the best antimicrobial effect were also tested against clinical isolates of resistant bacterial strains (*S. aureus*, *E. coli*, *A. baumanii*, *P. aeruginosa*). The results showed higher activity of the new AMPs compared to the control one, and the effect against *E. coli* was close to that of the control peptide.

An *in vivo* study was then conducted on the antimicrobial activity of one of the peptides in mice with *S. aureus* infection. The peptide has been administered by several routes of administration and only parenteral (*i.m.* and *i.p.*) routes of administration show no side effects. The tested peptide showed better performance compared to the starting one. The results demonstrate that the newly developed model represents a suitable way to discover new AMPs with high accuracy (39).

*Methods using deep learning.* The use of deep learning in the discovery of new AMPs contributes to the identification process because it allows the processing of a large volume of data from which to extract information about features and general characteristics.

Artificial neural networks (ANN). Fjell *et al*. used Quantitative structure–activity relationship (QSAR) research together with ANN for the discovery of new AMPs. At the beginning of their research, they selected a set of peptides with proven antimicrobial activity. Their 3D structure was investigated, and their QSAR descriptors were calculated. The descriptor and activity values of the peptides were then used in combination with the ANN to create models that were used to evaluate peptide sequences of potential efficacy. The validation of the method was performed by synthesis and *in vitro* testing of the peptides, which were predicted to exhibit activity. The antimicrobial activity of 18 peptides (13 from the group with expected high activity and 5 from the group with low activity) were investigated. Their MIC has been tested *in vitro* against some of the most dangerous and multidrug-resistant pathogens, including strains of multidrug-resistant *P. aeruginosa*, *Methicillin-resistant S. aureus*

*(MRSA)*, *E. cloacae* with derepressed chromosomal β-lactamase, extended spectrum β-lactamase (ESBL) producing *E. coli* and *K. pneumonia*, and *vancomycin-resistant E. faecalis* and *E. faecium*. Peptides with predicted high activity confirmed it by demonstrating a significant effect against the tested bacterial strains and show accuracy of 0.94 (40).

Convolutional neural networks (CNN). The Deep-AmPEP30 method is used for the detection of AMPs with a chain length of up to 30 AA. It uses a reduced dataset, deep convolutional neural networks (CNN) and reduced amino acid clusters (RAAC). RAAC groups amino acids according to their evolutionary information, substitution score, hydrophobicity and contact potential energy. This clustering approach improves the performance of the model created. In the particular study, the combination between CNN and RAAC increases the precision in predicting the activity of short-chain AMPs. The model was validated by being used to detect AMPs from the genome of *C. glabrata*, a commensal fungus that can be detected in gastro-intestinal tract. Deep-AmPEP30 selected a peptide consisting of 20 amino acids. Its activity has been confirmed experimentally, being comparable to ampicillin. The model predicted the antimicrobial activity of 30 peptides, showing accuracy of 0.77. Three of them with a chain length of 20, 24 and 29 amino acids, were studied for the manifestation of an antimicrobial effect. All three showed activity *in vitro* comparable to ampicillin against selected bacteria: Gram-negative (*V. parahaemolyticus*, *P. aeruginosa*, and *E. coli*) and one Gram-positive (*B. subtilis*) (41).

Recurrent neural networks (RNN). Long short-term memory (LSTM) models are a type of recurrent neural network (RNN) that have been used in research related to classification and generation of new AMPs. The study by Wang *et al*. focused on the discovery of sequences of potential AMPs with a chain length of up to 20 amino acids. The models used in the study were tested with sequences with proven low MIC, thus aiming for their higher efficiency. Another feature of the model is to search for peptides with possible activity only against *E. coli*. As a result of the study, the newly created LSTM and bidirectional LSTM (Bi-LSTM) demonstrate high accuracy (0.814 - 0.957), sensitivity (0.808 - 0.971), specificity (0.714 - 0.969) and area under the curve (82.3 - 98.2%) (42).

In 2022, Li *et al*. presented AMPlify – a model using deep learning to improve the process of *in silico* discovery of AMPs. At the heart of the model is Bi-LSTM which encodes the conformational information of the peptide. The model was initially trained with two data sets: one with known AMPs at the time of its creation, and the other with selected peptides that did not exhibit antimicrobial activity. Ensemble learning was used to improve the performance of the model, and it demonstrates high accuracy, 0.937. The study conducted by Li and his team differed from others because it did not use standard amino acids, but rather investigated the activity of peptides derived from multicellular organisms. In this case, the genome of the North American bullfrog (*Rana [Lithobates] catesbeiana*) was examined for the presence of currently unknown AMPs. The frog species was chosen because it is a known source of biologically active molecules. The antimicrobial activity study was conducted against several bacterial strains: *S. aureus* (ATCC 6538P), *S. pyogenes* (unknown strain; hospital isolate), *P. aeruginosa* (ATCC 10148), *E. coli* (ATCC 9723H and ATCC 29522), and a multidrug-resistant carbapenemase-producing New-Delhi metallobetalactamase (CPO-NDM) *E. coli* clinical isolate. Out of 11 potential AMPs 4 showed activity: RaCa – 1 against *E. coli* and *S. pyogenes*; RaCa - 2 and RaCa - 3 were effective against all tested bacterial strains, and RaCa - 7 inhibited the tested *E. coli* strains and showed low activity against *S. aureus* (43).

To address the challenges of deep generative models Das and his team created a framework that uses information about short-chain peptides available in the UniProt database. This approach facilitates the discovery of new molecules with a broad spectrum of action and low toxicity. The researchers propose Conditional Latent (attribute) Space Sampling (CLaSS), a simple, fast and extensive method to obtain targeted molecules, with accuracy between 0.668 and 0.943. As a result, 20 potential AMPs were discovered and synthesized in 48 days. In the *in vitro* testing of the newly synthesized molecules, 2 new short-chain peptides – YI12 (12 AA) and FK13 (13 AA) demonstrated activity against various pathogens (*S. aureus* (ATCC 29737), *E. coli* (ATCC 25922), *P. aeruginosa* (ATCC 9027), *A. baumanii*, *multidrug-resistant K. pneumoniae*, *polyR K. pneumoniae*). Both peptides showed no tendency to cause resistance in *E. coli*. Wet laboratory tests support the claim that the molecules have bactericidal activity, and microscopic studies, using a confocal microscope, show that the peptides have the ability to pass through bacterial cell membranes (44).

DL models included in the review show promising accuracy (average > 0.8) in predicting the activity of peptides with possible antimicrobial activity.

*Challenges and limitations of AI applications in combating AMR*

Despite the promising potential of AI in addressing AMR, several challenges and limitations must be acknowledged. One of the major limitations is data quality and availability. AI models rely heavily on large, high-quality, and well-annotated datasets. In the context of AMR, available data are often fragmented, heterogeneous, and biased toward specific geographic regions or healthcare settings,

which limits the robustness of developed models. Bias and generalizability represent additional concerns. Models trained on data from specific populations or institutions may not perform adequately when applied to different clinical environments, pathogens, or resistance patterns. This restricts the general applicability of AI-driven solutions in real-world clinical practice. Many AI-based approaches demonstrate promising results *in silico* or in experimental settings but lack prospective clinical trials and regulatory approval. As a result, their integration into routine clinical practice is still limited. Another important challenge is the limited interpretability of AI models, mainly using DL approaches. The "black box" nature of these models complicates their acceptance by clinicians and regulators, as understanding the rationale behind predictions is crucial for clinical decision-making.

## Conclusions

Artificial intelligence enables changes in the process of creating and discovering new drugs. It reduces the cost and time required to discover new molecules with potential antimicrobial activity. It can also be used to identify molecules of natural origin that can be applied in antibiotic therapy. AI can effectively use the data about the antimicrobial drugs obtained so far and based on it to discover suitable molecules to be included in antimicrobial therapy.

## Acknowledgement

Not applicable.

## Funding

Not applicable.

## Availability of data and materials

Not applicable.

## Ethics approval and consent to participate

Not applicable.

## AI use disclosure

During the preparation of this manuscript, the authors used Grammarly® for editing assistance and language improvement, specifically to improve spelling, grammar, word choice, readability, and clarity. The authors reviewed and revised all outputs from this tool and take full responsibility for the final content of the work.

## Conflict of interest

The authors declare no conflict of interest.

## References

1. Newman DJ, Cragg GM. Natural Products as Sources of New Drugs over the Nearly Four Decades from 01/1981 to 09/2019. J Nat Prod. 2020;83(3):770-803.
2. Strohl WR. The role of natural products in a modern drug discovery program. Drug Discovery Today. 2000; 5(2):39-41.
3. Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov. 2021; 20(3):200-216.
4. Dobson CM. Chemical space and biology. Nature. 2004; 432(7019):824-828.
5. Chen Y, Garcia De Lomana M, Friedrich NO, Kirchmair J. Characterization of the Chemical Space of Known and Readily Obtainable Natural Products. J Chem Inf Model. 2018; 58(8):1518-1532.
6. Pușcașu A, Gherghiceanu F, Andronic O. The use of artificial intelligence in drug discovery: from concept to current applications. Farmacia. 2025;73(1):33-39.
7. Saldívar-González FI, Aldas-Bulos VD, Medina-Franco JL, Plisson F. Natural product drug discovery in the artificial intelligence era. Chem Sci. 2022; 13(6):1526-1546.
8. Arghir IA, Rașcu Ștefan, Andronache IT, Ion I. Antibiotic resistance in post tuberculosis bronchiectasis exacerbations. Farmacia. 2025;73(5):1317-1325.
9. Chowdhury AS, Lofgren ET, Moehring RW, Broschat SL. Identifying predictors of antimicrobial exposure in hospitalized patients using a machine learning approach. J Appl Microbiol. 2020; 128(3):688-696.
10. Voermans AM, Mewes JC, Broyles MR, Steuten LMG. Cost-Effectiveness Analysis of a Procalcitonin-Guided Decision Algorithm for Antibiotic Stewardship Using Real-World U.S. Hospital Data. OMICS: A Journal of Integrative Biology. 2019; 23(10):508-515.
11. Boolchandani M, D'Souza AW, Dantas G. Sequencing-based methods and resources to study antimicrobial resistance. Nat Rev Genet [Internet]. 2019; Available from: www.nature.com/articles/s41576-019-0108-4
12. Macesic N, Polubriaginof F, Tatonetti NP. Machine learning: novel bioinformatics approaches for combating antimicrobial resistance. Current Opinion in Infectious Diseases. 2017; 30(6):511-517.
13. Khaledi A, Schniederjans M, Pohl S, Rainer R, Bodenhofer U, Xia B, et al. Transcriptome Profiling of Antimicrobial Resistance in Pseudomonas aeruginosa. Antimicrob Agents Chemother. 2016; 60(8):4722-4733.
14. Rodríguez-González A, Zanin M, Menasalvas-Ruiz E. Public Health and Epidemiology Informatics: Can Artificial Intelligence Help Future Global Challenges? An Overview of Antimicrobial Resistance and Impact of Climate Change in Disease Epidemiology. Yearb Med Inform. 2019; 28(01):224-231.
15. Weinstein ZB, Bender A, Cokol M. Prediction of synergistic drug combinations. Current Opinion in Systems Biology. 2017; 4:24-28.
16. Nava Lara RA, Aguilera-Mendoza L, Brizuela CA, Peña A, Del Rio G. Heterologous Machine Learning for

the Identification of Antimicrobial Activity in Human-Targeted Drugs. Molecules. 2019;24(7):1258.
17. Russell SJ, Norvig P. Artificial intelligence: a modern approach. Third edition, Global edition. Boston Columbus Indianapolis New York San Francisco Upper Saddle River Amsterdam Cape Town Dubai London Madrid Milan Munich Paris Montreal Toronto Delhi Mexico City Sao Paulo Sydney Hong Kong Seoul Singapore Taipei Tokyo: Pearson; 2016. p. 1132. (Prentice Hall series in artificial intelligence).
18. Xiang M, Cao Y, Fan W, Chen L, Mo Y. Computer-Aided Drug Design: Lead Discovery and Optimization. CCHTS. 2012;15(4):328-337.
19. Talat A, Khan AU. Artificial intelligence as a smart approach to develop antimicrobial drug molecules: A paradigm to combat drug-resistant infections. Drug Discovery Today. 2023;28(4):103491.
20. Bender A, Cortés-Ciriano I. Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 1: Ways to make an impact, and why we are not there yet. Drug Discovery Today. 2021; 26(2):511-524.
21. Fanelli U, Pappalardo M, Chinè V, Gismondi P, Neglia C, Argentiero A, et al. Role of Artificial Intelligence in Fighting Antimicrobial Resistance in Pediatrics. Antibiotics. 2020; 9(11):767.
22. Levine MM, Kotloff KL, Nataro JP, Muhsen K. The Global Enteric Multicenter Study (GEMS): Impetus, Rationale, and Genesis. Clinical Infectious Diseases. 2012; 55(suppl 4):S215-224.
23. Brintz BJ, Howard JI, Haaland B, Platts-Mills JA, Greene T, Levine AC, et al. Clinical predictors for etiology of acute diarrhea in children in resource-limited settings. Freeman MC, editor. PLoS Negl Trop Dis. 2020; 14(10):e0008677.
24. Brintz BJ, Haaland B, Howard J, Chao DL, Proctor JL, Khan AI, et al. A modular approach to integrating multiple data sources into real-time clinical prediction for pediatric diarrhea. eLife [Internet]. 2021;10. Available from: https://elifesciences.org/articles/63009
25. Gaynes R. The Discovery of Penicillin—New Insights After More Than 75 Years of Clinical Use. Emerg Infect Dis. 201; 23(5):849-853.
26. Teillant A, Gandra S, Barter D, Morgan DJ, Laxminarayan R. Potential burden of antibiotic resistance on surgery and cancer chemotherapy antibiotic prophylaxis in the USA: a literature review and modelling study. The Lancet Infectious Diseases. 2015; 15(12):1429-1437.
27. Paterson IK, Hoyle A, Ochoa G, Baker-Austin C, Taylor NGH. Optimising Antibiotic Usage to Treat Bacterial Infections. Sci Rep. 2016; 6(1):37853.
28. Goldstein J, Silberstein SD, Saper JR, Ryan RE, Lipton RB. Acetaminophen, Aspirin, and Caffeine in Combination Versus Ibuprofen for Acute Migraine: Results From a Multicenter, Double-Blind, Randomized, Parallel-Group, Single-Dose, Placebo-Controlled Study. Headache. 2006; 46(3):444-453.
29. Cheng F, Kovács IA, Barabási AL. Network-based prediction of drug combinations. Nat Commun. 2019; 10(1):1197.
30. Tran MH, Nguyen NQ, Pham HT. A New Hope in the Fight Against Antimicrobial Resistance with Artificial Intelligence. IDR. 2022; Volume 15:2685-2688.
31. Lv J, Deng S, Zhang L. A review of artificial intelligence applications for antimicrobial resistance. Biosafety and Health. 2021;3(1):22-31.
32. Smith NM, Lenhard JR, Boissonneault KR, Landersdorfer CB, Bulitta JB, Holden PN, et al. Using machine learning to optimize antibiotic combinations: dosing strategies for meropenem and polymyxin B against carbapenem-resistant Acinetobacter baumannii. Clinical Microbiology and Infection. 2020; 26(9):1207-1213.
33. Abdulla A, Wang B, Qian F, Kee T, Blasiak A, Ong YH, et al. Project IDentif.AI: Harnessing Artificial Intelligence to Rapidly Optimize Combination Therapy Development for Infectious Disease Intervention. Advanced Therapeutics [Internet]. 2020; 3(7). Available from: https://onlinelibrary.wiley.com/doi/10.1002/adtp.202000034
34. Booq RY, Tawfik EA, Alfassam HA, Alfahad AJ, Alyamani EJ. Assessment of the Antibacterial Efficacy of Halicin against Pathogenic Bacteria. Antibiotics. 2021; 10(12):1480.
35. Stokes JM, Yang K, Swanson K, Jin W, Cubillos-Ruiz A, Donghia NM, et al. A Deep Learning Approach to Antibiotic Discovery. Cell. 2020; 180(4):688-702.e13.
36. Hancock REW, Sahl HG. Antimicrobial and host-defense peptides as new anti-infective therapeutic strategies. Nat Biotechnol. 2006; 24(12):1551-1557.
37. Zasloff M. Antimicrobial peptides of multicellular organisms. Nature. 2002; 415(6870):389-395.
38. Brogden KA. Antimicrobial peptides: pore formers or metabolic inhibitors in bacteria? Nat Rev Microbiol. 2005; 3(3):238-250.
39. Wu X, Wang Z, Li X, Fan Y, He G, Wan Y, et al. In Vitro and In Vivo Activities of Antimicrobial Peptides Developed Using an Amino Acid-Based Activity Prediction Method. Antimicrob Agents Chemother. 2014; 58(9):5342-5349.
40. Fjell CD, Jenssen H, Hilpert K, Cheung WA, Panté N, Hancock REW, et al. Identification of Novel Antibacterial Peptides by Chemoinformatics and Machine Learning. J Med Chem. 2009; 52(7):2006-2015.
41. Yan J, Bhadra P, Li A, Sethiya P, Qin L, Tai HK, et al. Deep-AmPEP30: Improve Short Antimicrobial Peptides Prediction with Deep Learning. Molecular Therapy - Nucleic Acids. 2020;20:882-894.
42. Wang C, Garlick S, Zloh M. Deep Learning for Novel Antimicrobial Peptide Design. Biomolecules. 2021; 11(3):471.
43. Li C, Sutherland D, Hammond SA, Yang C, Taho F, Bergman L, et al. AMPlify: attentive deep learning model for discovery of novel antimicrobial peptides effective against WHO priority pathogens. BMC Genomics. 2022; 23(1):77.
44. Das P, Sercu T, Wadhawan K, Padhi I, Gehrmann S, Cipcigan F, et al. Accelerated antimicrobial discovery via deep generative models and molecular dynamics simulations. Nat Biomed Eng. 2021; 5(6):613-623.