Artificial Intelligence on the Battle Against Multidrug Resistant Bacteria

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ABSTRACT

The third greatest cause of death worldwide is antimicrobial resistance (AMR), a hidden epidemic. The pipeline for developing antibiotics is limited, despite the excessively high rate of AMR. Artificial Intelligence (AI) is a game-changing method that speeds up drug development due to its rapidity, cost-effectiveness, reduced labor needs and decreased failure rates. There is potential for effectively predicting and identifying AMR in bacteria with the use of AI. Additionally, the process of discovering novel antimicrobials may be sped up by combining lab testing with machine learning (ML) techniques. Although the use of AI/ML in clinical settings is still relatively new, developments in algorithm development and data quality indicate that broad clinical use is soon to follow. This chapter will provide a current summary of how AI is affecting the fight against AMR.

I. INTRODUCTION

Antibiotic research began with the discovery of penicillin, which transformed how bacterial infections are treated in modern medicine. However, the misuse and overuse of antibiotics in livestock and human medicine, together with insufficient infection prevention and management strategies, have led to the global increase of antimicrobial resistance (AMR) [1-3]. By 2025, AMR is predicted to cost the global economy more than 100 billion dollars and account for 10 million deaths, ranking third in the world in terms of annual mortality [4]. The focus and financial shift away from AMR during the Coronavirus 2019 (COVID-19) pandemic, together with the careless use of antibiotics, may have potentialized AMR [5]. Antimicrobial resistance arises naturally by genetic mutation and spreads by horizontal gene transfer, primarily through conjugation but also infrequently through transformation and transduction [6]. Although antibiotics are crucial in the fight against bacterial diseases, the misuse and widespread availability of these medications have caused AMR to spread faster than the development of new antibiotics, leading to multidrug-resistant (MDR) bacteria. A worldwide catastrophe has resulted from this circumstance, with fewer safe antibacterial alternatives available to fight MDR bacteria in the health system [7]. Therefore, it is imperative to focus efforts on research and adopt new legislation to control the AMR pandemic A multidisciplinary approach, as well as creative tactics and technology, are necessary to address the complex problem of AMR and guarantee that infectious disease therapies are successful. The first step in addressing the AMR dilemma would be to identify MDR bacteria promptly and effectively. This step would limit antibiotic usage by providing tailored prescriptions based on proper MDR identification and discovering new strategies for combating AMR. Herein lies the role of artificial intelligence (AI), one of the innovative methods used for fast and precise AMR identification [8]. AI simulates human intellect, decision-making, and problem-solving skills by combining computer science and large, reliable data sets. The technology is an effective instrument for preventing AMR, accelerating and enhancing traditional procedures and tactics, guaranteeing a smart, digitalized healthcare system and patient care, and lowering human error [9]. Importantly, antimicrobial susceptibility test analysis and interpretation using AI-driven software are crucial, particularly in low- and middle-income (LMIC) nations with restricted access to medical personnel and specialists [10]. A subset of artificial intelligence known as machine learning (ML) uses experimental data, commonly called training data, to create a learned model that allows a computer to predict specific events [11]. A component of ML is deep learning (DL). Several databases, including MegaRES and CARD (Comprehensive Antibiotic Resistance Database) [12], gather peer-reviewed information on AMR determinants, such as bacterial species, description of the mode of action on the antibiotic class, and the appropriate DNA and protein sequences. Algorithms might be trained using these data to create a learned model that can accurately detect known orunknown AMR and even forecast the minimum inhibitory concentration (MIC) of MDR bacteria [13]. Incorporating AI and ML into healthcare settings enables proactive treatments and focused antimicrobial stewardship by extending beyond predictive modeling to real-time monitoring, decision support systems, and drug development [14, 15]. For example, antimicrobial peptides (AMPs) optimization has been potentialized by computational modeling, providing new treatments against MDR bacteria [16]. This chapter focuses on the role of AI in creating an effective healthcare system that supports early, accurate, and cost-effective disease detection, enhances the prescription of antibiotics, and discovers new medications to combat AMR. The limitations and difficulties of AI in AMR-focused drug development are also covered, along with ethical issues. Using AI to its full capacity expedite the search for new antimicrobial medicines, improve available drugs, and successfully tackle the rising danger of AMR.

**II. BACKGROUND**

AMR is a natural occurrence in which bacteria, viruses, fungi, and parasites acquire the capacity to withstand medications intended to eradicate them. The development and spread of AMR have been facilitated by the abuse and overuse of antibiotics in human medicine, animal husbandry, and the environment. These practices make once-effective medicines useless, which raises death rates, prolongs illnesses, and increases healthcare expenses. Therefore, AMR poses a major worldwide hazard to human health that needs to be addressed urgently. According to the World Health Organization's (WHO) Global Antimicrobial Resistance and Use Surveillance System, AMR is becoming more prevalent and is already one of the main causes of mortality worldwide [17]. Bacterial AMR was responsible for 1.27 million deaths worldwide in 2019 [17]. Western sub-Saharan Africa had the highest resistance-related all-age mortality rate, with 27.3 deaths per 100,000 people (20.9–35.3) [17]. In the U.S., antimicrobial resistance to at least first-line antibiotics causes over 2 million illnesses annually and at least 23,000 fatalities, according to the Centers for Disease Control and Prevention (CDC) [18]. The Infectious Disease Society of America has designated six pathogens as "ESKAPE" organisms, which are the most dangerous to human health because of their rapidly increasing antibiotic resistance: *Enterococcus fecium*, *Staphylococcus aureus* (*S. aureus*), *Klebsiella pneumoniae* (*K. pneumoniae*), *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterobacter* spp. [19]. In China, AMR has also emerged as a public health issue. The rate of carbapenem-resistant Gram-negative bacterial resistance has significantly increased, according to the Chinese Antimicrobial Surveillance Network [20]. Notoriously, between 2005 and 2022, the prevalence of carbapenem-resistant *A. baumannii* increased from 39.0 to 71.9%, whereas the prevalence of carbapenem-resistant *K. pneumonia* increased from 2.9 to 24.2% [21]. Methicillin-resistant *S. aureus* has also been detected often in recent years, with a high detection rate of about 30% [21]. Over the past ten years, the number of newly researched and authorized novel medicines has steadily declined; between 2010 and 2014 [22], just four new antibiotics were licensed, leaving clinics with few alternatives for treating AMR. Interestingly, most antibiotics were found by screening soil microorganisms for secondary metabolites with antibacterial properties [23]. Regrettably, the rediscovery problem—in which the same compounds are discovered repeatedly—is making it harder to find new antibiotics [24]. Therefore, the need for clinical therapy cannot be met only by novel medication discovery. In computer science, AI refers to the development of intelligent computers that objectively perform activities that normally demand human-like intellect [25]. AI technologies facilitate scientific discoveries by presenting unique techniques and becoming integrated into several fields, including drug development and clinical research process [26]. AI has consistently played a key role in coordinated multidisciplinary efforts to address the AMR dilemma.

**III. THE CONTRIBUTION OF AI TO AN EFFECTIVE HEALTHCARE SYSTEM**

A. **AI Expedites the Diagnosis of Infections Caused by Bacteria** The diagnosis of healthcare-associated infections (HAIs) depends on early infection detection, also known as nowcasting. The monitoring of nosocomial infections (Moni-ICU) in intensive care units classifies patients as "normal," "borderline infected," or "definitely infected" based on clinical factors, including heart rate compatibility and decreased blood pressure against blood stream infections [27]. To distinguish between viral and non-infectious sepsis as well as the systemic inflammatory response syndrome (SIRS) in critically sick infants, Lamping and collaborators created a random-forest (RF) model utilizing eight commonly identified criteria [28]. This approach was superior to identification based on biomarkers. During the COVID-19 pandemic, Rawson and colleagues created an ML model to identify bacterial co-infection [29]. The program made predictions based on regularly accessible blood test data. All of these screening methods reduce the need for unnecessary antibiotic prescriptions while also enabling early patient treatment.

B. **AI Enhances Antibiotic Prescribing and Disease Diagnosis** A careful prescription of antibiotics necessitates precise and accurate methods to determine the etiology of a pathology. The Global Enteric Multicenter Study (GEMS) provided clinical and quantitative molecular etiologic data for developing a prediction model based on logistic regressions and RF that predicts the etiology of viral diarrhea and, consequently, lowers the improper prescription of antibiotics [30]. Using a specificity of 0.85 and sensitivity of 0.59, this non-laboratory model predicts viral diarrhea based on five clinical factors: lower age, dry and cold season, nutritional status shown by increased height, absence of bloody diarrhea, and vomiting [30]. Google has created a DL system that uses chest radiographs to identify active pulmonary TB [31]. Interpreting chest radiographs calls for specialized knowledge that is not always accessible, particularly in LMICs, where most TB cases are recorded. This model displayed an 88% sensitivity in detecting active TB, better than any radiologists in the trial. Additionally, this detection technique decreased the cost of TB detection by 40–80% for each patient who tested positive [31].

C. **AI Assists in the Interpretation of Antimicrobial Susceptibility Test** The antibiotic susceptibility test (AST) is an essential metric for examining how bacteria react to antimicrobial treatments. It is crucial to comprehend a patient’s AST profile to develop an accurate and customized treatment plan. Most commonly, the Kirby-Bauer disk diffusion test is employed [32]. A human mistake frequently occurs in the interpretation of antibiograms since it depends on the knowledge of the technicians. Despite the introduction of several automatic reading technologies, they are costly and infrastructure-dependent. Although hospitals and clinics in LMICs face the greatest challenges with AMR [33], it is challenging to make these costly technologies available in such countries. Interestingly, AI-powered smartphone applications (apps) for antibiogram interpretation guarantee an easy-to-use method for comprehending the AST profile. For example, an offline smartphone app using AI was created by Médecins Sans Frontières to decipher disk diffusion ASTs from an AST picture [34]. This app utilizes a rule-based expert system that combines machine learning and image processing. The app is a simple software that assists users at every stage and just needs a basic Android smartphone, making it appropriate for usage in LMICs [34].

D. **AI Investigates a Massive Amount of Information in Electronic Patient Data in Intensive Care Unit (ICU)** Interestingly, AI plays an important role in ICUs. Several options for applying AI in the emergency sector have been investigated. A vast amount of data saved in electronic patient records has been examined using non-administrative AI techniques. Numerous artificial intelligence models have been developed to extract important information from a person's outline and identify important patient outcomes [35]. Algorithms related to administered AI have shown their use in radiography, pathology, and histology due to their proficiency in automated example acknowledgment of reports [36]. According to mechanical technology, AI is widely used in many medical fields, particularly in cardiology and surgery, to identify cardiac arrest or failure, and in oncology to classify cancer types and stages of development [37]. Although AI in intensive care units is still in its infancy, research has successfully assessed its application in treating patients in critical condition. Numerous AI systems have been used to study the length of hospital stays, the incidence of death, readmissions to intensive care units, and the risk factors for developing unanticipated illnesses like sepsis. An AI-based technique was created in a prior study to predict hospital admission days and patient survival using information from 14,480 patients [38]. With an area under the curve of 0.82, the model predicted a longer stay. This is in contrast to a clinical investigation that found that physicians were around 55% accurate in estimating the length of an ICU stay [39]. Using physiological values obtained during the first 48 hours of ICU admission, a hidden Markov framework correctly predicted the length of stay in the ICU [40]. The critical condition of patients in intensive care units necessitates the rapid and accurate evaluation of raw, high-dimensional inputs in the form of text, statistics, photos, and other data. Determining complex, nonlinear connections between the data is also necessary. Patterns in data have been represented as mathematical equations using a variety of statistical approaches [41]. A "best-fit line" is suggested by linear regression. Rather than reducing the link to a mathematical formula, DL treats complex medical data like a physician would carefully weigh the available facts to reach a logical conclusion. In contrast to a single clinician, DL can capture and assess several inputs at once, enabling the creation of prediction models based on the intended outcome. Along with other AI approaches related to healthcare, ICU applications employ three DL techniques: the recurrent neural network (RNN), convolution neural network (CNN), and deep belief network (DBN). Steenkiste and collaborators used a temporal computational model with a bidirectional long short-term memory (LSTM) and nine clinical factors evaluated over time from a high-quality database of 2,177 intensive care unit patients to forecast the outcome of blood culture tests [42]. When the interval between an anticipated occurrence and the diagnosis is unknown, this type of DL algorithm performs well. The average area under the curve (AUC) for the network was 0.82, whereas the area under the receiver operating characteristic curve was 0.99. Additionally, the findings showed that forecasting is only feasible with a slight decrease in predictive strength, even several hours before the occurrence [42].

**IV. ACCELERATING ANTIBIOTIC DISCOVERY IN THE ARTIFICIAL INTELLIGENCE ERA**

Halicin gained international recognition as the first antibiotic discovered using AI [43]. By combining empirical research and *in silico* predictions, Stokes and collaborators discovered halicin, a novel broad-spectrum antibiotic that effectively inhibits the development of *Escherichia coli* [44]. The results of screening over 2,300 compounds to learn if they would suppress *E. coli* growth were used to train a deep neural network (DNN) that predicts antimicrobial activity based on compound chemical structures [44]. The c-Jun N-terminal kinase inhibitor SU3327, subsequently renamed as halicin, was predicted and further verified as a strong inhibitor of ESKAPE and multidrug-resistant organisms using the ML model, which was applied to the Drug Repurposing Hub. In mouse models, halicin demonstrated growth inhibitory activity against infections caused by pan-resistant *Acinetobacter baumannii* and *Clostridium difficile*. The same ML technique was used to further search over 107 million molecules in the ZINC15 database, and eight probable antibacterial compounds that vary structurally from known antimicrobials were found. Two of these compounds were broad-spectrum antibiotics that might target many genes in *E. coli* that confer resistance to antibiotics [44]. A predictive ML algorithm based on the Online Chemical Database and Modeling Environment (OCHEM) detected six moderately hazardous chemicals and one nearly innocuous anti-TB compound [45]. AI models have discovered several antibiotics and antibiotic alternatives, including but not limited to antibiotics from antimicrobial peptides, beta-lactamase inhibitors, antibiotics from nonribosomal peptides, antibiotics from marine natural products, de novo drug designing, combination therapy optimization, and antibiotics from bacteriocins [46]. Table 1 shows some of the AI alternatives against AMR.

**Table1: AI alternatives against AMR**

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| --- | --- | --- |
| **Applications of AI in AMR** | **Benefits** | **Disadvantages** |
| Novel antibiotics | ▸Shorter production duration▸Focused broad-spectrum bioactivity ▸Economical | ▸Educate libraries about the necessary pharmacokinetic characteristics of medications▸Select the best strategy, reducing toxicity, and finding lead compounds |
| Antimicrobial peptides | ▸Various action pathways▸Low likelihood of AMR▸Simplicity of synthesis using DL and ML | ▸Elevated toxicity▸Costly to produce on a big scale▸Undesirable for general usage▸Prone to allergic responses |
| The anticipated severity of infection | ▸The effectiveness of differentiating between▸ infectious and noninfectious disorders ▸Availability of decision support▸Decrease in mortality | ▸Difficult accurate data collection▸Lack of pertinent laboratory information. |
| Proper prescribing of antibiotics | ▸Decisions and reviews of antibiotic prescriptions are automatically supported ▸Feedback is automatically entered and pertinent improvements are made▸Operation direction | ▸Operational bias |

A. **Identifying Beta-lactamase Inhibitors Using AI**

Parvaiz and collaborators discovered promising extended spectrum b-lactamase (ESBL) CMY-10 inhibitors that showed *in vitro* susceptibility against MDR clinical isolates (e.g., E. cloacae, E. alvei, and *E. agglomerans*) and ATCC strains (e.g., *Escherichia coli*, *Enterobacter cloacae*, *Enterobacter agglomerans*, and *Enterobacter alvei*). Interestingly, through the use of Ligand Competitive Saturation (SILCS) technology, the functional group binding patterns of class C beta-lactamase CMY-10 were mapped. Through pharmacophore screening of 700,000 compounds utilizing site identification by ligand competitive saturation (SILCS-MC), ligand-grid free energy (LGFE) analysis, and ML-based RF scoring techniques, the acquired Frag-Maps information was utilized to find ligands with comparable functional groups [47].

B. **Identifying Antibiotics from Antimicrobial Peptides Using AI**

Higher-order species produce AMPs, now known as host defense peptides (HDPs), which are naturally occurring short chains of amino acids (usually 12–50 amino acids) used to combat invasive microbes. Higher-order species produce AMPs, now known as host defense peptides (HDPs), which are naturally occurring short chains of amino acids (usually 12–50 amino acids) used to combat invasive microbes. AMPs are potential next-generation antimicrobial medicines used as a last-resort antibiotic. The last few years have seen the development of several computational techniques to produce possible antimicrobials from a variety of AMPs that have the lowest toxicity and the least tendency to develop AMR. A single-hidden-layer feed-forward neural network with 64 specified features, RF models, support vector machine (SVM), and discriminant analysis are models used in the AMP prediction module of the Collection of Antimicrobial Peptides (CAMP) database [48]. An ML model trained with several 12-amino acid AMPs was created by Wu and collaborators to assess the contribution of the amino acids at each position to the total antibacterial activity. This model revealed DP7, a new 12-amino acid AMP with an antibacterial action against Staphylococcus aureus that is drug-susceptible and drug-resistant [49]. Guava-derived AMP, Guavanin2, was discovered to have antibacterial action by the ML-based genetic algorithm. Guavanin2 exhibits antibacterial efficacy against a variety of *in vivo* infections [50]. Using an unsupervised global model trained on all known short peptide sequences from the UniProt database, Das and colleagues identified, manufactured, and experimentally tested 20 AMPs in 48 days. High potency against both Gram-positive and Gram-negative bacteria, including MDR Klebsiella pneumoniae, was demonstrated by two of these AMPs. These AMPs exhibited minimal toxicity and a low tendency to cause drug resistance in *E. coli* [51]. Two antimicrobial peptides with bacteriostatic properties against *S. aureus* and *E. coli* were predicted by an adaptive sparse neural network [52]. In contrast to fully linked networks, sparse network models are less precise. Artificial neural network (ANN) and inductive chemical descriptors based on two sizable 9-mer peptide libraries were used in an atomic-based quantitative structure–activity relationship (QSAR) model to identify the host defense peptides (HDPs) HHC-10 and HHC-36 against superbugs (e.g., Gram-positive and Gram-negative bacteria). The AMP prediction method, Deep-AmPEP30, uses CNNs to predict AMPs that are 30 amino acids long [53]. To predict short AMPs (less than or equal to 30 amino acids), Deep-ABPpred uses word2vec in conjunction with bi-directional long short-term memory (Bi-LSTM) [54]. Wang and collaborators created brief, new AMP sequences with antibacterial activity against *E. coli* by combining an LSTM generating model with a bidirectional LSTM classification model [55]. Sequences up to 200 amino acids may be handled by the DNN classifier AMP Scanner Vr.2, which is based on embedding, convolutional, max pooling, and LSTM recurrent layers [56]. Multi-head scaled dot-product attention (MHSDPA) and a hidden layer of context attention (CA) are two techniques that make AMPlify an attentive DL model for enhanced in silico AMP synthesis. AMPlify discovered four new putative AMPs that have antibacterial efficacy against strains of *E. coli*, including MDR carbapenemase-producing *E. coli*, and *Pseudomonas aeruginosa* [57].

C. **Identifying Antibiotics from Nonribosomal Peptides Using AI**

Recently, natural microbial products have been used by the scientific community to discover new drugs. Though little is known about the genes that encode them, nonribosomal peptides (NRPs) are naturally occurring sources of cytostatics, pigments, siderophores, toxins, anticancer agents, immunosuppressants, and antibiotics [58]. Biosynthetic gene clusters (BGCs) coordinate the synthesis of NRPs. BGCs are clusters of thousands of nucleotide genes that encode NRP synthetases (NRPSs) and multi-modular proteins. In an NRPS BGC, a number of NRPS modules with an adenylation (A) domain are responsible for identifying, activating, and integrating a particular amino acid into the finished product. Several ML-based programs, including NP.searcher [59], PRSM4 [60], NRPSpredictor2 [61], SANDPUMA [62], web server SeMPI [63], GARLIC [64], and the antiSMASH pipeline, are available for predicting NRP products from microbial genomes. These genome-mining programs are predictors of substrate specificity that have been trained using a collection of A domains with established specificities. Due to variations in gene order, macrocyclization of the linear peptide sequence of BGCs, and uncertainties in the assembly line's A domain order, it is difficult to accurately anticipate the NRP structure from genomic data. As a result, mass spectra data or chemical structure databases are needed to validate genome-based predictions. A new computer technique called Nerpa is used to find new BGCs that encode NRPs in a high-throughput manner [65]. Through a scan of 13,399 typical bacterial genomes from the reference sequence (RefSeq) collection against 8368 known NRPs, it connects 117 BGCs. It compares bacterial draft assemblies and whole genomes to an NRP database, which includes a database of putative NRPs (pNRPdb). Nerpa overcomes ambiguous predictions by using the substrate's stereochemistry, methylation status, and specificity prediction score. It detects known NRPS BGCs, including stephensiolide and ohmyungsamycin, that are absent in minimum information about a biosynthetic gene cluster (MIBiG). In comparison to GARLIC, it is 15 times quicker, uses three times less memory, and has two times lower false discovery rates (FDRs) when revealing novel BGC-NRP linkages [65].

D. **Identifying Antibiotics from Bacteriocins Using AI**

Gram-positive bacteria produce peptides called bacteriocins through ribosome synthesis as a competitive self-defense. Since bacteriocins have a limited killing spectrum, they are prospective antibiotic substitutes with a lower risk of antibiotic resistance. They exhibit antimicrobial activity via several methods, including biophysical interactions with the target bacterial membrane facilitated by the peptide's charge, hydrophobicity, and shape. It is challenging to isolate bacteriocins and verify them *in vitro*, though. Bacteriocin sequences that have been experimentally confirmed and annotated are found in the databases BAGEL and BACTIBASE. AntiSMASH is a genome-mining technology frequently utilized in the identification of bacteriocins [60]. Bacteriocin Operon Associator (BOA) was created by Morton and collaborators to discover bacteriocin via homologous searches of genes related to transport, immunity, regulation, and post-translational modifications related to bacteriocin [66]. Among other ribosomally synthesized and post-translationally modified peptides (RiPPs), RiPPquest employs mass spectrometry data to identify bacteriocins [67]. RiPPquest has been improved upon by MetaRiPPquest. Fields and colleagues created an ML-based pipeline that combines sequence-free bacteriocin prediction with a straightforward biophysical trait filter to produce 20 amino acid peptides for developing bacteriocin-derived drugs and in silico verification. This model detected peptides that were highly effective against *P. aeruginosa* and *E. coli* [68].

E. **Identifying Antibiotics from Marine Natural Products Using AI**

Marine organisms produce a wide variety of secondary compounds that are physiologically active and have antibacterial properties, referred to as marine natural products (MNPs). Fifty thousand chemicals from terrestrial and marine microorganisms and macroorganisms are included in the AntiMarin database. A model that predicted potential antibiotic activity from MNPs was created using SVM, RFs, and Classification Trees (CTs) [69]. Using naïve Bayesian, SVM, recursive partitioning (RP), and k-nearest neighbors (kNN), Wang and collaborators discovered 12 novel anti-methicillin-resistant *S. aureus* (MRSA) compounds. The highly resistant MRSA strains ST239, ST5, and ST252 were used in a cell-based experiment using the broth microdilution technique to confirm the effectiveness of all the antibiotics [70].

F. **Using AI Against Biofilm**

Biofilms contribute to resistance to antibiotics. It results from a genetic mutation and an increased number of microorganisms, which encourages the horizontal transmission of resistance genes. Globally, MRSA is a major cause of nosocomial infections. Typically, biofilm-associated infections caused by *S. epidermidis* are persistent. Although new tactics to fight biofilms have recently emerged, they are challenging to be implemented. Opportunities are presented by ML to address the pressing need to find antibiofilm agents. Unsupervised ML predicted that chemical components obtained from nonbiocidal essential oils would modulate the generation of biofilms in strains of *P. aeruginosa*, *S. aureus*, and *S. epidermidis* strains, hence avoiding drug resistance [70, 71].

G. **Using Machine Learning to Find New Antibiotic Resistance Predictors**

The growing issue of AMR has given rise to ML/AI techniques. These technologies allow systems to track epidemic tendencies, forecast resistance, examine bacterial genomes, and find novel vaccinations or antibacterial medications [36, 72]. Antibiotic resistance can be predicted using genomic content, patient history, and infectious characteristics thanks to access to genome sequences and worldwide surveillance data (55). To optimize medicines, ML is excellent at identifying the factors that contribute to resistance, such as resistance-associated genes [73], resistance-associated alleles [74], and treatment circumstances [75]. Nowadays, much research uses ML algorithms to forecast antibiotic resistance using gene mutations, gene presence or absence, and antibiotic sensitivities as training data. Many research studies predict the antibiotic resistance status of bacteria using rule-based or ML techniques based on the genetic content, patient demographics, and treatment history. Numerous investigations have found encouragingly high prediction accuracies, frequently over 90% [13]. For instance, Khaledi and collaborators [74] used whole-genome sequencing (WGS) in conjunction with transcriptomics to find a panel of biomarkers to make precise predictions, achieving great sensitivity (> 90%) in predicting resistance in *Pseudomonas aeruginosa* clinical isolates. In comparison to conventional bacterial identification and antibiotic resistance testing methods, Wang and colleagues [76] demonstrated over 90% accuracy in predicting antibiotic resistance in *Staphylococcus aureus* bloodstream infections and received resistance predictions up to 6 hours faster. New technologies, such as matrix assisted laser desorption ionization-time of flight mass spectrometry (MALDITOF) mass spectrometry, have further shortened the time required to forecast antibiotic resistance, which could enhance patient outcomes and antibiotic stewardship [77]. A retrospective analysis showed that 89% of the antibiotic regimens would have been altered by swiftly predicting antibiotic resistance using MALDI-TOF. This would have directly improved antibiotic stewardship and possibly resulted in quantifiable improvements in patient outcomes. Machine learning is essential for detecting epistatic interactions that may result in resistance. For instance, missense mutations in the rpoB gene responsible for encoding the β-subunit of RNA polymerase induce rifampicin resistance, a prevalent issue among infectious disorders brought on by Mycobacteria, Pseudomonas, and Staphylococcus. These changes decrease the affinity of the proteins that make up the RNA polymerase complex, which in turn lowers the nucleic acid affinity of the complex. The development of resistance to the antibiotic rifampicin in a specific bacterial strain may be predicted by a computer model developed by Portelli and collaborators [78]. Since sequenced isolates cannot generate precise predictions unless the genetics of resistance are well established beforehand, the identification of these epistatic combinations or even uncommon mutations granting resistance may be missed in present evaluations. To discover genes whose involvement in resistance has been well-characterized or to predict antibiotic resistance brought on by known resistance genes, machine learning has become more popular [76]. For a *de novo* resistance prediction system to be trained correctly, a sizable dataset containing the genomes and related antibiotic susceptibility test results from resistant and susceptible isolates is needed. Susceptibility testing is used to ascertain if antimicrobials inhibit the development of the bacteria or fungi that cause a certain illness. Whole genome sequencing (WGS) and regular antimicrobial susceptibility testing enable previously unheard-of genotype-to-phenotype mapping. Machine learning systems may then be trained using this data to identify the best course of action for newly discovered illnesses brought on by the same organism. Clinically derived isolates have been used to educate machine learning algorithms and offer the most complete examples to discover the range of alterations that permit effective infection. The fact that a wide range of mutations are discovered during infection [79, 80] that might not be directly causing AMR is a possible drawback of relying solely on clinical isolates to assess resistance. For instance, ML predictions may be confused by mutations frequently reported in clinical isolates that contain genes related to bacterial adaptability to the host's harsh and shifting surroundings. Genes involved in immune evasion, nutrient acquisition, metabolic changes, reactive oxygen species (ROS) tolerance, extracellular polysaccharide formation to form biofilms, development of small colony variants, hypermutator strains, and ultimately AMR are frequently found to have mutations in clinical isolates. Our capacity to pinpoint the genes that directly contribute to AMR in vivo is hampered by these mutations, which permit bacterial adaptability during infection. Genetic noise may also result from the isolates' high genetic diversity. According to research that has identified many predictors with no obvious connection to antibiotic resistance, this genetic noise may weaken the categorization of predictors from the ML algorithms or find predictors that are a consequence of infection rather than resistance itself [81]. Using in vitro evolution trials against a range of drugs is one potential strategy to counteract genetic noise in clinical isolates. It is possible to detect the in vitro mutational spectrum on the selective pressure that contributes to AMR by doing these studies with a large number of duplicates [82].

**V. Antimicrobials as Phage Therapy, AMPs, and Small Compounds**

AI is a potent weapon in the fight against AMR [83, 84]. Data-driven techniques, for instance, can be used to forecast new antibiotic compounds and image-based techniques can assist in identifying bacteria that are resistant to antibiotics [85]. The rapid identification of more promising antimicrobial compounds can be facilitated by AI-assisted compound library screening or the design of new compound structures. The foundation for creating more effective antibiotics can also be laid by the ability of AI to predict possible resistance sites and associated enzymatic functions using known data, such as genomic data [58]. Additionally, AI has made peptide design and synthesis, synthetic aperture radar (SAR) evaluation, target identification and dynamic modeling, and medication repurposing easier [86]. In the sections that follow, antimicrobials will be divided into four main categories: phage therapy, AMPs, and small compounds.

A. **AI in the Creation of Small-Molecule Antibiotics**

The screening of secondary metabolites produced by soil microbes with antibacterial qualities used to be the main technique for discovering new antibiotics, particularly during the 1950s and 1960s, which is referred to as the "golden age of antibiotic discovery" [87]. The rediscovery problem, regrettably, hindered the success of this strategy, and in subsequent eras, the vast majority of newly created antibiotics with clinical use were categorized as analogs of already-existing bacteria groups. Due to the widespread occurrence of current resistance determinants, these analogs' long-term effectiveness was challenged [23]. Pursuing novel chemotypes with MOAs that are noticeably different from those of currently available antibiotics should be the ideal goal of new antibiotic discovery. These substances have a higher chance of avoiding current resistance factors, which means they will continue to be useful over time. Fortunately, AI technologies have been accelerating this process in several ways. This section will cover four areas of AI-facilitated small-molecule antibiotic discovery: chemical library screening, protein structure–function-guided drug rational design, therapeutic repurposing, and identification of biosynthetic gene clusters (BGCs).

*Development of Small Molecule Antibiotics by BGCs*

Numerous secondary metabolites with the potential to develop into novel antibacterials are encoded by BGCs, which operate as natural repositories [88]. However, the fact that many BGCs are members of species that cannot be cultivated in a lab setting limits their ability to reach their full potential. BGCs may be cryptic or transcriptionally quiet, even for those culturable. As a result, there is a high demand for genome mining-based in silico BGC prediction. AI has been becoming more significant, even if conventional rule-based systems like Antibiotic Resistant Target Seeker (ARTS) [89] and Antibiotics and Secondary Metabolite Analysis Shell (antiSMASH) [90] have previously demonstrated remarkable success [88]. DeepBGC predicted the chemical activity of products and found new BGC classes using a DL algorithm [91]. To forecast ribosomally produced and posttranslationally changed peptides, another DL-based technique called DeepRiPP combined genomic and metabolic data [92]. Contrarily, PRISM 4 was able to predict the chemical structures of the secondary metabolites—from which the activities can be deduced—using the BGC's sequence information. Walker and colleagues [93] also achieved precise activity prediction by integrating resistance marker profiles with BGCs.

*Antibiotic Testing Driven by MOA*

The size of the chemical library limits conventional drug screening, which frequently fails to identify the MOA of the hits. Johnson and collaborators [94] conducted a primary chemical screen on *Mycobacterium tuberculosis* hypomorphs (mutant strains depleted in essential targets) to overcome these constraints and create a novel paradigm known as PROSPECT (primary screening of strains to prioritize expanded chemistry and targets). More than 8.5 million chemical-genetic interaction profiles were produced as a result, and supervised learning helped identify a higher number of inhibitors against crucial targets like DNA gyrase and folate metabolism [94]. Furthermore, the investigation of vast chemical regions *in silico* is made possible using ML-based screens. Consequently, this significantly raises the likelihood of discovering structurally and functionally unique molecules with strong antibacterial qualities. Liu and colleagues [95] used growth inhibition data from approximately 7,500 FDA-approved compounds to train a message-passing deep neural network on *Acinetobacter baumannii*, a nosocomial pathogen known for drug resistance. This network subsequently identified aubacin, a narrow-spectrum antibiotic with a novel MOA targeting lipoprotein trafficking.

*AI in Medication Development and Protein Structure Prediction*

AI-based methods can support the logical design and optimization of medications in addition to searching for new secondary metabolites and screening current chemical libraries. Understanding the three-dimensional structure of a pharmacological target and, frequently, its protein-protein interactions form the foundation of rational design. Even though protein structures are still best determined experimentally, this method is low-throughput and technically difficult for many proteins. Thankfully, Deep-Mind's neural network AlphaFold2 transformed this by achieving near-experimental accuracy in structure prediction for most proteins [96]. RoseTTAFold, a three-track neural network for structure prediction developed by Baek and collaborators [97] and inspired by the ideas of AlphaFold2, showed accuracy that was comparable to AlphaFold2. Additionally, RoseTTAFold makes it possible to predict protein-protein interactions straight from protein sequences, negating the necessity for docking and subunit structure prediction [97]. Wong and collaborators [98] used molecular docking simulations with structures of the E. coli essential proteome predicted by AlphaFold2 and hundreds of active/inactive antibacterials to apply these potent tools for antibiotic discovery. They also evaluated the model performance using *in vitro* enzymatic assays. Sadly, the area under the receiver characteristic curve (AUROC) of 0.48 indicated that it performed poorly on average across 12 key targets; this was ascribed to the docking technique rather than AlphaFold2 predictions. A substantial boost in AUROC was achieved by refining the docking calculations using a variety of ML-based scoring methods to enhance performance [98]. The answer lies in enhancing ligand binding poses predicted by docking simulations to AlphaFold2 models since this suggests that there are still major obstacles to reliably predicting how drug candidates attach to their targets, even with the assistance of AlphaFold2 [98].

B. **AI in the Discovery of AMP**

According to their antimicrobial properties, AMPs are a class of structurally varied short peptides that work through a range of mechanisms. They usually include a few to hundreds of amino acid residues in their sequence, with or without further modifications [99]. It is suggested that AMPs target cell membranes because they can bind and damage zwitterionic and negatively charged membranes, ultimately causing membrane permeabilization. Due to their unique MOA, AMPs are positioned as a novel class of possible antibacterial medications, which probably makes resistance development difficult [99].

*AMP Mining in Virtual and Extinct Sequence Space*

There are more sources of AMP mining besides microbes. Maasch and colleagues [100] created panCleave, a random forest model that can anticipate proteome-wide cleavage sites to search for AMPs encrypted inside extinct and extant human proteomes, based on the idea of "molecular de-extinction." In both murine skin abscess and thigh infection scenarios, lead AMPs discovered by panCleave demonstrated membrane permeabilization and anti-infective effectiveness against *A. baumannii*, underscoring the potential of the paleoproteome as a therapeutic candidate repository [100]. Regardless of the source, AMP mining from pre-existing proteomes is inherently skewed toward the sequence space that the proteome confines. Huang and collaborators [101] created a sequential model ensemble pipeline made up of machine learning modules with a coarse-to-fine design approach to mine the whole virtual library of peptides with lengths ranging from six to nine amino acids. This allowed them to explore the full space of peptide sequences. This pipeline's discovery of three lead hexapeptides shows strong effectiveness against clinical isolates resistant to many drugs in both in vitro and in vivo settings, demonstrating the enormous potential of sequential model ensemble pipelines for objective peptide screening tasks [101].

C. **AI in the Development of Phage Treatment**

Phage treatment is one of the alternative tactics that have been crucial in the fight against antibiotic resistance, along with small-molecule drugs and AMPs [102]. An essential component of the human microbiome, bacteriophages are naturally occurring predators of bacteria that have coevolved with their bacterial hosts for 3.8 billion years [103]. Phage treatment offers far higher specificity than antibiotics, which are mostly broad-spectrum drugs. This reduces disruptions to the microbiota and stops the spread of AMR caused by antibiotics [104]. Numerous instances of therapeutic effectiveness have previously been documented [105, 106].

*The Identification of Phage*

The crucial function that viruses play in a variety of ecosystems has been highlighted by recent developments in metagenomic sequencing [107]. Innovative AI-driven techniques for the discovery, annotation, and analysis of viral sequences within intricate metagenomic datasets have been created in response to this expanding relevance [108]. For example, Seeker is a DL-based tool that quickly identifies a variety of bacteriophages, even when their sequences are only slightly comparable to those of recognized phage families [109]. Beyond conventional viral identification systems, VIBRANT uses a hybrid machine learning and protein similarity technique to automatically recover, annotate, and evaluate the metabolic implications of viruses in metagenomic assemblies [110]. Additionally, VirSorter2 combines several classifiers to detect a wide variety of viruses with high precision, greatly improving the accuracy and breadth of viral sequence recognition in metagenomic datasets [111]. Furthermore, PhageBoost, a brand-new feature space-based machine learning technique intended for quick and widespread prophage discovery, greatly improves bacteriophage identification [112]. A multimodal tool called DEPhT is designed to find, accurately extract, and annotate phages in Mycobacterium genomes. This allows for thorough comparative genomic investigations by effectively differentiating between bacterial and phage sequences [113]. Additionally, Phanta is a master at virome-inclusive gut microbiome profiling, using thorough gut viral genome catalogs and k-mer-based classification techniques to swiftly and precisely quantify prokaryotes and viruses, greatly enhancing viral species identification over assembly-based techniques [114].

*Prediction of Phage Host*

The discovery of phage host species is crucial for improving therapeutic applications and comprehending viral-host relationships. To tackle this problem, creative computational techniques have been created. VirHostMatcher-Net is a versatile network-based architecture that incorporates alignment-free similarity metrics and CRISPR sequences, dramatically increasing the range of known virus-host interactions and improving host prediction accuracy [115]. With a predictive efficiency of over 90%, the creation of a computational model based on genome analysis allows for the effective prediction of phage-bacterium interactions [116]. Additionally, a knowledge graph and graph convolutional network are leveraged by HostG, a semi-supervised learning model, to improve host prediction for novel viruses, providing the useful capability of predicting hosts from unknown taxa [117]. Together, these methods help us understand the interactions between viruses and their hosts and investigate the potential uses of bacteriophages in other fields.

*Prediction of Phage lifestyle*

There are two distinct lives that bacteriophages may lead: virulent and temperate. The virulent lifestyle has important ramifications for phage treatment. Phage lifecycle prediction is important but still difficult, particularly for phages built from metagenomic data. Novel AI-driven strategies have been developed to overcome this problem. With an astounding 99% accuracy rate, PHACTS (Phage Classification Tool Set) classifies phages into virulent or temperate groups using a supervised random forest classifier and a unique similarity algorithm [118]. Simultaneously, BACPHLIP (BACterioPHage LIfestyle Predictor) predicts the lifestyle of bacteriophages using conserved protein domains and a random forest classifier, achieving an exceptional 98% accuracy [119]. PhaTYP (Phage TYPe prediction tool) also achieves exceptional performance in accurately predicting the lifestyles of phages from short contigs by using Transformer's Bidirectional Encoder Representations, a contextalized embedding model inspired by natural language processing [120].

**VI. THE SIGNIFICANT IMPACT OF AI ON ANTIBIOTIC STEWARDSHIP PROGRAM (ASP)**

The significance of an antimicrobial stewardship program (ASP) has been demonstrated by several studies. The statistics unequivocally show how important an ASP is in lowering antibiotic misuse and the collateral harm that frequently follows from excessive antimicrobial usage [121, 122]. Additionally, the statistics show that an ASP results in an infection prevention plan. There have been disastrous outcomes as a result of the growing danger of AMR brought on by improper medication practices [123]. According to the Centers for Disease Control and Prevention (CDC), there are over 35,000 individual deaths and 28 lakh cases of antibiotic-resistant infections every year in the U.S. alone [124]. Furthermore, in 2017, the CDC recorded 223,900 cases of Clostridium difficile, with around 13,000 fatalities [125]. To adopt ASPs, the Centers for Medicare and Medicaid Services (CMS) now required hospitals and assisted living facilities [126]. The outpatient setting does not, however, have this necessity. According to available data, the majority of research supporting the advantages of an ASP has focused on hospital settings, which has limited the information available on the benefits of an ASP in outpatient settings. Implementing outpatient ASPs may be challenging due to several challenges. Limited resources include the inability to manage data across various electronic health systems and pharmacies, a lack of staff with knowledge of infectious diseases and antibiotics, as well as a lack of funding, support, and infrastructure. Time limits for work that would not otherwise be reimbursable might be additional challenges. If an ASP does not raise financial advantages or potentially result in extra expenses for their practice, clinicians are unwilling to invest the time necessary to implement it [127]. Pharmacists, doctors, patient and provider education initiatives, and systems for data recording, reporting, and intervention may all be a part of a standard ASP program. Since the number of patient visits or procedures determines the current CMS- and relative value unit (RVU)-based payment models, spending time on nonprocedural and nonpatient-specific activities may unintentionally impact doctors' bottom lines [128]. At least 30% of antibiotic prescriptions in outpatient patients, according to the CDC, are unnecessary. Most outpatient clinics, however, lack the resources necessary to implement the appropriate strategies. This endeavor has also been neglected since medical practices have not been encouraged to participate in outpatient ASPs. In 2016, the National Infection Prevention Strategy Ambulatory Medical Care Survey found that only 3% of patient visits were to facilities connected to medical or academic health centers, while over 60% of visits were to practices with five or fewer practitioners in the U.S. [129]. Finally, 89.7% of patient visits happened at establishments classified as private practices. Despite the statistics on the misuse of antibiotics in outpatient settings displayed by the CDC, initiatives that address the need for an ASP in outpatient settings have not been consistently modified. For the concepts of an ASP to have a major influence on lowering the threat of AMR, they must be utilized in both inpatient and outpatient settings. Moreover, an ASP in an outpatient context needs to be created in a way that many institutions may easily and effectively modify, irrespective of the facilities' funding, and approvals.

**VII. DIFFICULTIES IN USING AI ON DRUG DISCOVERY**

Although technology has advanced quickly in the last ten years, finding new antibiotics is still challenging. Scientific journals are overflowing with reports of AI-based drug discovery, which has resulted in the issue of dereplication, or the repeated discovery of the same chemical. Significant data are required for AI-based models, which might be expensive. Furthermore, it is yet uncertain how an AI algorithm will be concluded. The most popular approach to drug discovery, target-based, has not yet produced many fruitful outcomes [130]. Since in silico methods are less costly than wet-lab methods, many medications are being discovered using AI and ML, but only a small percentage of antibiotics found in silico make it to clinical trials. based models, which might be expensive. Furthermore, it is yet uncertain how an AI algorithm will be concluded. The most popular approach to drug discovery, target-based, has not yet produced many fruitful outcomes [130]. Since in silico methods are less costly than wet-lab methods, many medications are being discovered using AI and ML, but only a small percentage of antibiotics found in silico make it to clinical trials.

**VIII. FINAL CONSIDERATIONS**

The method of discovering new antibiotics with the least expense, effort, time, resources, and likelihood of antibiotic resistance has been transformed by AI. The technology investigates many domains as potential drug sources, including AMPs, NRPs, bacteriocins, and MNPs. It is nearly challenging to manually extract a medication with zero AMR risk from large data, and as next-generation sequencing grows, so does the amount of data that can be recovered. Given the potential promise of AI technologies for AMR, researchers have been employing AI to perform a variety of straightforward and repetitive activities that might significantly increase research efficiency. However, AI has specific drawbacks. First, the limited amount of data makes it difficult for current AI models to anticipate high-dimensional traits, which leads to reduced accuracy. Thus, future research should focus on automated annotation of unlabeled data using unsupervised learning. Second, present AI-based systems are not sufficiently generalizable since they can only analyze datasets with the same distribution. As a result, few-shot learning and transfer learning will be used more and more in the future to fight AMR. Antimicrobial resistance is a complicated issue that goes beyond the creation of novel medications and treatments since it is caused by the improper usage of antibiotics. A cooperative and integrated teaching strategy about the appropriate use of antibiotics by the general public and healthcare professionals is also necessary to address this issue. Importantly, AI holds promise as a tool to identify effective antibiotic substitutes.

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