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ARTIFIAL INTELIGENCE IN ANTI MICROBIAL RESISTENCE REVIEW; NOVEL TARGETS, DRUG REPURPOSING AND THERAPEUTIC INNOVATION

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Abstract:

Antimicrobial resistance (AMR) has become a problem for public health all over the world. This issue makes it harder to treat infections with the medicines we already have. The fast growth of germs that are resistant to drugs has made it important to find new ways to create medicines that fight these infections. Artificial intelligence, machine learning and deep learning is getting a lot of attention as a way to help with these problems. This review shows how artificial intelligence is being used in research about resistance. It focuses on finding targets for drugs discovering new medicines and using old drugs for new purposes. Artificial intelligence helps look at sets of data from genes, proteins, molecules and patients to find patterns that show resistance. It also helps predict how well a medicine will work and check if new treatments are good. Using intelligence to find new uses for existing medicines can save time and money in making new drugs. Some medicines like halicin, auranofin, ebselen and ciclopirox have shown promise in fighting germs. Also, artificial intelligence helps design molecules test them virtually and make predictions to find and improve medicines. With these improvements there are still problems, with the data how well the models can explain their results making sure they work checking for side effects and getting them to patients. Overall combining intelligence with traditional ways of making medicines offers good chances to speed up finding new medicines and create new ways to fight antimicrobial resistance.

Keywords: *Antimicrobial resistance, Artificial intelligence, Machine learning, Deep learning, Drug discovery, Drug repurposing, Novel antimicrobial targets, Therapeutic innovation.*

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INTRODUCTION:

Antimicrobial resistance (AMR) is a natural occurrence microorganism such as bacteriaantibiotics in human medicine, animal agriculture and the environment have enhanced the Acute situation and spread of AMR. Thus, AMR is a serious and foremost global threat to human health that requires practical actions urgently. The Global Antimicrobial Immunity and Use Monitoring System Implemented by the World Health Organization (WHO) revealed that AMR is on the rise and already a leading cause of death. This leads to the Infectiousness of treatments that ware previously effective, and to leading to long lasting illness, increased mortality rates, and higher healthcare costs. Globally, it was inferred that, in 2019 alone, approximately 4.95 million deaths were linked to bacterial AMR, with 1.27 million deaths Particularly Characteristics to bacterial AMR The maximum all-age death rate due to resistance was identified in Western sub-Saharan Africa, with 27.3 deaths per 100,000 individuals (20.9–35.3) Based on the data from the Centres for Disease Control and Prevention Assessment, AMR to at least first-line finding antibiotics accounts for more than two million ,infections in the US alone each year and at least 23,000 deaths.(1)

The Serious treat of antimicrobial resistance is of specific importance in the category of antibiotic resistance in bacteria. According to the CDC, more than two million people in the United States become ill with antibiotic-resistant diseases every year, resulting in least of 23,000 deaths. Antibiotic resistance impairs a human immune system's ability to fight infectious diseases and also promotes to different adverse outcomes in sensitive patients receiving chemotherapy, dialysis, surgery, and joint replacement. Moreover, people with chronic conditions like diabetes, asthma, and rheumatoid arthritis will be heavily affected by antibiotic resistance. Since the effectiveness of antibiotics will be reduced due to sustained presence in trends of AMR, physician'sefficacy last-resort classes of medicine such as carbapenems and polymyxins, which are not necessarily easily obtainable in developing countries, have a high cost, and have many different side-effects. One of the most well-known cases of AMR, Methicillin resistance in staphylococcus aureus (MRSA), has been related with high dearth rate rates every year across the globe. In addition, multi-drug-resistant gram-negative bacteria (MDR-GNB) has made the treatment of different infections like pneumonia and urinary tract infections more challenging. Furthermore, drug resistance to tuberculosis, gonorrhoea, and typhoid fever are increasing every year and considerably contribute to the high costs of individuals health as well as the health care systems around the world, particularly in developing countries. Currently, 4.1% of new tuberculosis cases are considered to be multi-drug resistant. In countries like India, the Philippines, Russia, and South Africa, which have always had a high number of TB cases compared to other parts of the world, multi-drug-resistant TB is predicted to notably by 2040. (2)

Artificial intelligence or AI is a branch of computer science that focuses on building machines that can do tasks requiring human- thinking in a logical way AI tools are now being used in scientific areas. They are helping speed up discoveries, in medicine. In drug development AI is helping scientists find medicines faster and make the whole process from research to clinical use more efficient. This is especially true in the fight against resistance. AI is now a part of efforts to solve the growing problem of antimicrobial resistance in this review we will look at the state of antibacterial drugs in both clinical and preclinical stages. We will also examine AI-based methods in antibiotic development with a focus, on designing new drugs improving their chemical structures and finding new ways these drugs work against bacteria. Machine learning has been used in ways for AMR. For example, AMR is studied through sequence-based AI applications see references AI has been used to design antibiotics and to create synergistic drug combinations see references.AI plays a key role in AMR prediction. (3)

Machine-learning algorithms analyse data on use and resistance and predict which microorganisms will develop resistance to specific drugs. Machine-learning algorithms help healthcare providers and policymakers make used for surveillance of resistance see reference Machine-learning models analyse amounts of data on antimicrobial use and resistance and identify emerging resistance patterns and potential AMR hotspots. Machine-learning models help public health authorities respond to outbreaks of infections more quickly and effectively. For stewardship machine learning is used to optimize antimicrobial use in healthcare settings for example by finding the best combination of drugs for a particular infection or, by predicting which patients risk developing a resistant infection see reference Machine learning can help reduce the burden of AMR.(4)

This comprehensive review examines transformative role of AI in AMR, stressing their applications in resistance prediction, and diagnostic innovation, and the improvement of antibiotics.(5)

OVERVIEW OF ARTIFIAL INTELLIGENCE IN DRUG DISCOVERY

AI is a branch of computer science that focuses on creating machines that mimic intelligence. These machines can understand, learn, process language recognize patterns solve problems and make decision. AI includes specialized areas; each

designed for specific tasks. These areas include computer vision, expert systems, robotics, natural language processing, neural networks, fuzzy logic and machine learning. Machine learning or ML uses algorithms to carry out tasks and gets better over time by learning from data inputs. The learning process in AI and ML does not stop with training data or time. It keeps improving as more data is fed into the system. This ability to handle datasets makes AI and ML very effective in tackling global challenges related to antimicrobial resistance (AMR) AI and ML models can analyse data in a rational way. They can detect trends predict outcomes and support decision-making with accuracy. This makes them tools, in scientific research and healthcare applications.[6]

The commonly used AI/ML approaches supervised learning algorithms, unlabelled learning algorithms, underpinning learning (RL), and deep learning (DL) frameworks. Supervised learning algorithms utilize classified data such clinical record and microbial genomics, to predict results and judgments. For example, Supervised machine learning has detected genomic indicators associated with antibiotic sensitivity in *Escherichia coli* across various sequence types (STs). These genetic markers clarify how STs develop and propagate within communities that are likely to promote dissemination likewise, it was used to estimate *Streptococcus pneumoniae* sensitivity to β-lactam antibiotics by associating penicillin-binding protein (PBP) sequences with minimum inhibitory concentrations (MIC) measurements unsupervised learning algorithms do not rely on previously labelled or categorized data, instead focusing on independently identifying clusters and patterns within datasets. This approach can uncover new insights and hidden connections within microbial communities and resistant strains for example, a recent study used unsupervised learning and identified the simultaneous presence of antibiotic resistance and metal resistance in *Salmonella enterica*

Reinforcement learning utilizes trial-and-error feedback to identify the most suitable drug combination or antimicrobial treatment approaches for resistant bacterial strains, even with Restricted information about bacterial population Behaviour For example, a recent study used this technique for the treatment of sepsis, offering most appropriate antibiotic combination and duration that in accordance with clinical practices DL techniques such as convolutional neural networks (CNNs) and recurrent neural networks (RNNs) are utilized to recognize complicated patterns in data. CNNs can identify antibiotic susceptibility trends from genome analysis while RNNs are able to of forecasting antimicrobial resistance from time-series data The selection of AI and ML methods relies on the type of data source and specific aims of the analysis.[7]

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ML strategies have been used in drug discovery over the past 15–20 years with expanding complexity. The most latest aspect of drug development where Beneficial change from AI/ML is gradually developing, is in clinical study planning, Implementation and evaluation. The COVID-19 pandemic may further enhance adoption of AI/ML in clinical trials due to a greater dependence on digital technology in clinical trial conduct. As we move towards a world where there is a growing combination of AI/ML into R&D, it is essential to get past the related buzz-words and noise. It is equally important to understand that the scientific method is not outdated when making conclusions about data. Doing so will help in distinguishing expectations from publicity and lead to informed evidence- based decisions the most effective application of AI/ML in drug development. This manuscript aims to clarify main principles, describe applications and finally offer findings and a fair perspective on the optimal use of AI/ML Methods

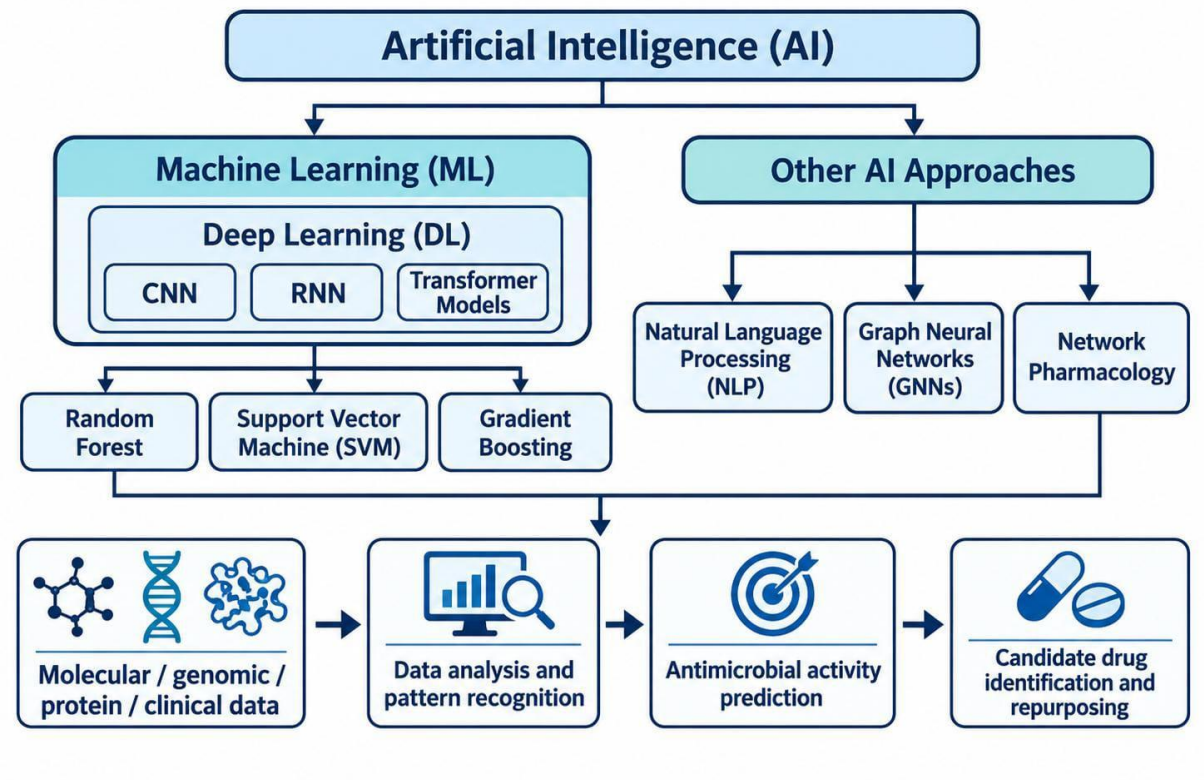

Figure 1: Types of Artificial Intelligence

Artificial Intelligence (AL)

AIprogressivelyapplied in drug repurposing to alloworganised, large-scaleestimation of possible antimicrobial compounds against MDR disease causing microorganisms. It includes a collectionof computer-basedtechniques, incorporating ML, DL, GNNs, network pharmacology (an AI-adjacent, network-based approach), and NLP, each offering differentabilities for detecting and selecting suitable for repositioningmedicines through the combination of molecular, genome-related, protein-related, and clinical information, thus expandingexaminationexceeding the restrictions of conventional in vitro testing. [10]

1.Machine Learning (ML)

Supervised ML computational methods, involving random forests, support vector machines, and gradient boosting, are commonly employed to represent structure–activity relationships andforecast antimicrobial capacity from molecular features. Developed on data collection of recognizedeffective and ineffective compounds, ML models can detectmolecular propertieslinked with antimicrobial activity; their major benefit is explainability, as feature-importance analyses can demonstrate molecular motifs related to effectiveness. However, ML methods remain

sensitive to dataset systematic error and uneven distribution, which can causeexcessive model fitting or decreased generalisability, making robust cross-validation, data augmentation, and ensemble modelling vital to model robustness.[11]

2.Deep Learning (DL)

Deep learning methods are part of machine learning. These methods include neural networks, recurrent neural networks and transformer models. These models can learn high-dimensional information about chemical structures and biological interactions. They need little help, from manually created features. CNN models can take fingerprints or graph-based embeddings to predict if a substance has antimicrobial activity. Transformer models use sequences of chemical information to make better predictions. Even though these deep learning models perform well they are not easy to understand. This makes it hard to use them in real-world situations. To fix this problem explainable AI methods have been created. These include attention visualization and SHAP which stands for Shapley Additive Explanations. Some models that look at substructures have helped find a type of antibiotic.[12]

APPLICATIONS OF AI IN PHARMACEUTICAL RESEARCH

Although machine learning deep learning and artificial intelligence are sometimes used in the way they are actually in a hierarchy. The big idea of intelligence is the imitation of human intelligence by computer systems. This includes tasks, like learning, reasoning and understanding language. It also includes showing information or knowledge. Artificial intelligence is the use of a computer to copy behaviour with very little or no human help. Artificial intelligence technologies have changed the way drugs are developed and found.[13]

1.AI in Drug Discovery and Development

Artificial intelligence is modifying how new medicines are identified and created. By March 2023, Deep Pharma Intelligence had reported at least 14 fully AI-generated drug prospects in clinical trials. Generative models can now generate practical artificial data with the properties scientists need, and AI is being used to detect leads and leads, evaluate medical drug targets more quickly, and improve drug configurations. existing drug progress stays slow and costly partly because it lacks modern tools, a limitation AI can help reduce. AI models can also link a compound's molecular structure to its biological function, which lets researchers developed candidates with enhanced potency, selectivity, and suitable pharmacokinetics. One-shot learning combined with refined long short-term memory (LSTM) architectures has shown excellent predictive capabilities even where data are limited. Because drug development must also satisfy standards for safety, therapeutic effectiveness, and cost, these unmet needs have made AI a promising approach. integrating computational design with conventional medicinal chemistry therefore provides a solid base for future research.[14]

2.Target Discovery

Deep learning and AI have substantially changed target discovery The process involves ranking candidate targets, identifying which ones responsible for disease progressing, and assessing therapeutic relevance. Because human diseases are complicated, it often requires integrating multiple datasets to understand disease mechanisms and patient-specific differences Since harmfulness and inadequate treatment effectiveness are the leading causes of clinical failure, it is important to create a link between a target RNA (or RNA-protein complex) and the disease at the very start of a program. [15]

3.preclinical research

Estimating the toxicity of compounds at an early stage is important. Cell-based tests that are done using animal studies can make costs go up a lot and online tools like LimTox, pkCSMadmetSAR. Toxtree can help reduce those costs. Drug development is affected by diseases that have no treatment or by medicines that're not strong enough or are harmful. AI and machine learning models help with finding and checking compounds, identifying targets making peptides analysing toxicity and physical and chemical properties tracking drugs checking how well they work and using them in ways. In pharmacokinetics and pharmacodynamics AI models can predict values simulate how drugs move in the body and get removed and improve the way drugs are given, which is better, than old-style experiments.[16]

4.Machine Learning Algorithms

Machine learning (ML), a subdivision of AI, lets machines improve through practice instead of direct coding. Its methods detect trends and associations between data and results. ML has long been applied in drug identification, applied research, and preliminary studies, but its utilization in clinical studies activities and data evaluation has been delayed over the past two periods because of the additional complication involved. traditional computational methods contain Naïve Bayes, decision trees (DT), and hidden Markov models (HMM). The later development of artificial neural systems permitted machines to group and arrange data in a way loosely simulated on the human brain, advancing AI further. Guided learning is the most common method in medicine. An algorithm is educated on annotated data and identifies the

connection between predictor and response variables. A common process separates the data collection into a learning data set (70-80%) and an evaluation data set (20-30%).[17]

5. Data Analytics

Data can be analysed with many evaluation techniques, involving pattern extraction and AI. Large scale data analytics can expose abnormalities that arise when huge quantities of data from various origins are merged. Improved electronic storage, new gathering techniques, and rapid computers and computational procedures now enable rapid evaluation of extensive, changing information system. Visual data analytics uses data as its subject of analysis. In food hygiene, for example, knowledge the data sources, characteristics, and analysis activities support researchers select relevant analysis and visual representation methods for investigating dangers. The processing capacity necessary for large unified datasets must also be taken into account, and if applicable, models should be developed to operate concurrently.[18]

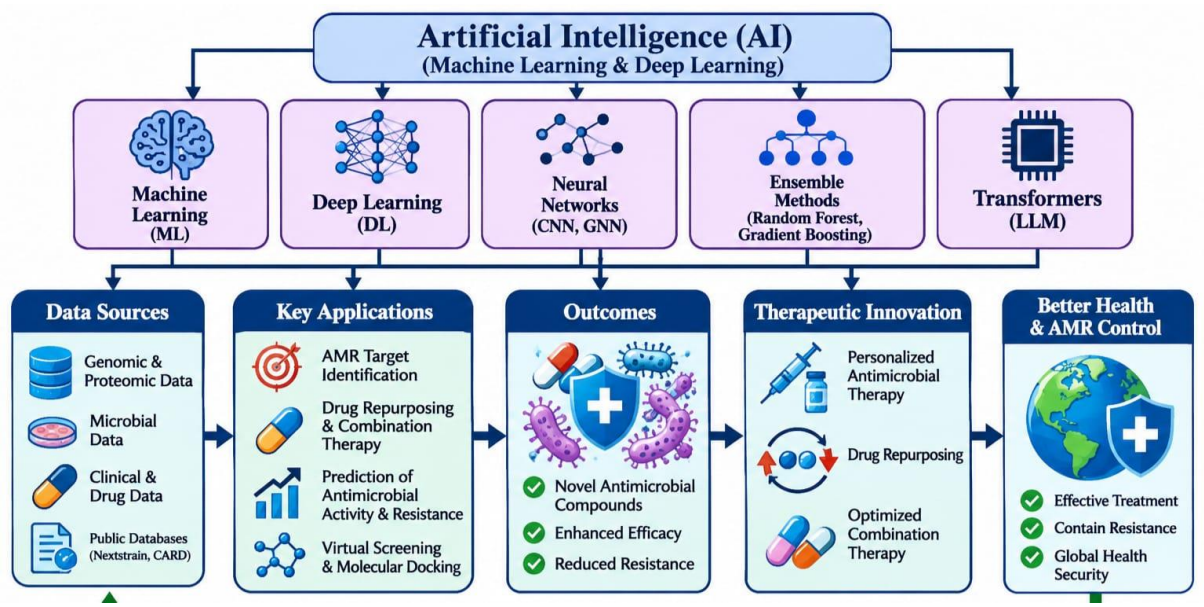

Figure2:Overview of Artificial intelligenceand Their Applications in Antimicrobial Resistance Research

ROLE OF AI IN IDENTIFICATION OF NOVEL DRUG TARGETS AND ANTIMICROBIAL COMPOUNDS

The Extensive use of antibiotics promoted the development of antibiotic-resistant bacteria, leading to a raising infection burden. In the WHO European Region, antimicrobial resistance (AMR) is directly associate with for 133 000 deaths each year and contribute to 541 000 deaths. Thus, infection by drug-resistant bacteria may become critical, causing worldwide mortality in the future and posing a risk to human freedom, privacy, and health. However, financial support in antimicrobial drug research and development has declined, largely due to limited financial motivation lack of sustainable commercial strategies.During the period of major scientific advancement of the 1940s, alarge proportion antibioticwas identified via the Waksman Platform. The Waksman platform involves a systematic process which soil-originating bacteria are isolated, the microbial colonies are examined for antibacterial effectiveness, and the biological active microbial compounds are subsequently purified. Although this approach has been extremely effective for nearly two decades, difficulties in the isolation and purification steps have made it less practical in recent years. Additionally, extensivecompound collections for screening antimicrobial agents [used as a general term referring to antibiotics and antimicrobial peptides (AMPs)] have restricted structural diversity for drug development, and no new antimicrobial agent classes have been discovered through this method since 1980. It is difficult to yield novel chemical frame works utilizing these conventional methods, and to avoid identifying known compounds.In the over recent decades, researcher have investigated antimicrobial agents via a several different approaches, such as screening of naturally occurring compounds, automated large –scale screening, evolution and phylogenetic based and genetic relationship analysis, structure-guided rational design, as well as innovative methods such as the is chip – based microbial isolation and resistance-guided discovery of new antibiotics. Computer-assisted compound screening (VS) and molecular docking are also used because the above methods are extremely costly and expensive and labor– intensive.Artificial intelligence (AI) technologies have advanced the

pharmaceutical and research and development to speed up identification of new antimicrobial compounds Machine learning (ML) and deep learning (DL) computational model, such as protein structure prediction, virtual screening, toxicity prediction, pharmacophore modeling, drug repositioning, and clinical monitoring, have been utilized to drug discovery. In these fields, they can reduce costs.[19]

Increase efficiency, and improve the speed and accuracy of drug design. The structural characteristics of antibacterial agents tend to follow recognizable physicochemical and pharmacophoric patterns, making them recognizable and extractable using AI. The presence of large-scale antimicrobial data collection, containing minimal inhibitory concentration (MIC) values across various microbial strains, supplies important informationfor an AI model. AI modeling provides an approachof identifyingmolecular structurebiologicalactivity relationships from complicated chemical and biological information. Predictive computational models canprioritize potential compounds based on antibacterial activity, while generative models expand the search space by designing new structures in addition to those available existing libraries. Through the combination of chemical information science, bioactivity information, and advanced ML approaches,these approacheshelp in moreefficient identification of new chemical frameworks and potential mechanisms of action.[20]

AI BASED IDENTIFICATION 0F ANTIMICROBIAL RESISTANCE

Prior to the application of AI for detection, AMR was identification by sequence comparison against databases via computational analysis or by using antibiotic susceptibility testing (AST). Using these methods, a large numerous of genuine resistance-associated factor with rather distinct sequences to currently known AMR would be classified as non-AMR (incorrect negatives). Moreover, the bacterial cultivation in AST is time intensive and certain bacteria, such as B. Forsyth us, are challenging to cultivate in vitro (Wade 2002; Macesic et al. 2017). The in computational approach via the use of ML offers an alternative approach a to accurately detect previous and new AMR in a rapid, user-friendly and effectiveapproach(Arango-Argoty et al. 2018; Lingle and Santerre 2019). All of the computational model this article utilizes a supervised MLtechniques+, in which the algorithm is developed using training datasets with that have been annotated with labels to generate a learnt model. Subsequently, the algorithm could process unseen datasets and perform automated classification with their own annotation.[21]

Recognition using antimicrobial-resistant protein (ARP)

Compared with identification of resistance genes based on DNA data, this part explains to the prediction methods that use protein structure information to identify AMR determinants. The pairwise comparative modelling (PCM) algorithm the frequency a protein is partly similar to the previously identified resistance – associated proteins and non-resistance –associated protiens. It could identify a correctly associated protein resistance -although the sequence similarly was less than 20% to known ARP because proteins sharing similar biological roles usually have preserved functional regions. However, this algorithm is limited by a increased rate of false- positive predictions since similar protein structures do not perform identical biological function.The game-theoretic-dynamic-weighting-based-feature-evaluation (GTDWFE) algorithm is an represent an advancement the PCM algorithm (Ru. The GTDWFE algorithm considers the composition, physiochemical, this algorithm considers the mutual -relationship between each of the pre-selected features such as 3D arrangement and water-repelling characteristics and their role in bacterial AMR. This algorithm successfully detected novel and unknown AMR proteins with prediction accuracy ranging from 93–99%accuracy. However, the major limitation of GTDWFE is the reliance on existing information of protein sequence and their function. Moreover, the feature relationship and weightage information used may not be applicable to predict ARP in Gram-positive bacteriaspecies.[22]

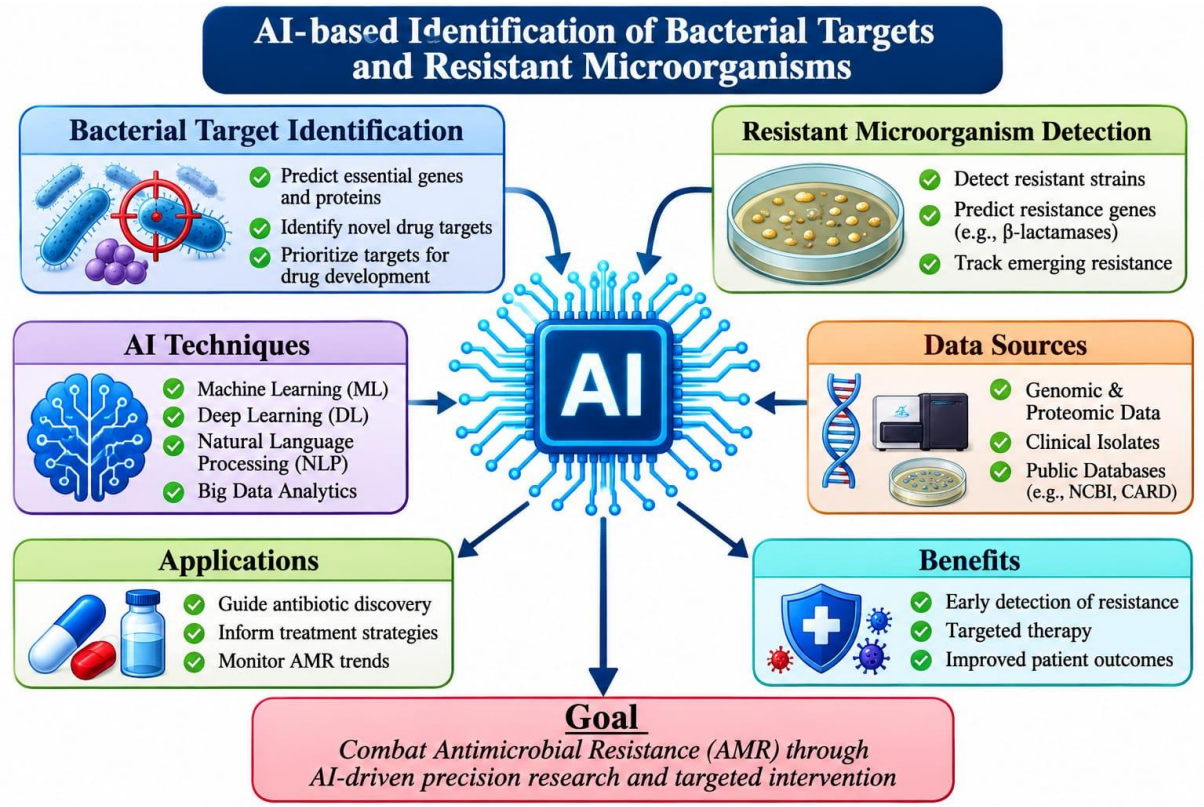

Figure 3:AI -based Identification of Bacterial Targets and Resistant Microorganism

TARGET VALIDATION AND GENOMIC/PROTEOMIC DATAANALYSIS

Target validation in antimicrobial resistance [AMR] using artificial intelligence refers to the process of using computational model and machine learning to conform that a specific biological molecule, [such as enzyme or pathogens and cell wall compounds] is both essential for the microbe's survival anddruggable.[23]

Genomic approaches for antimicrobial resistance

The genomic is a play a key data sources this type of analysis contain a high-quality, representative, and diverse genomic data, phenotypic AMR data, and relevant related diseased surveillance metadata. Investigation and surveillance of AMR using genomics methods have initially focused on separate field, such as human health or animal health

Long-read genomic sequencedata

Long-read genome sequencing data improve AMR research and surveillance due to its ability to recognize and define complicated define mechanisms This allows for exact determination of the genetic background of resistance genes and mobile genetic elements. furthermore. lo. Long-read sequencing may also identify unique resistance factors that may be overlooked by short-read sequencing methods. but, while the base detection precision, of Oxford Nanopore Technology (ONT) sequencing has enhance greatly since its beginning, it may still not be enough for some applications, suchas detail examination of genetic difference. moreover, frequentchanges of guidelines and data collections make it hard to run ONT an ISO-certified diagnostic testing setting with high legal for steady and reliable technologies. thus, caution must be exercised to enhance sequence quality (including best variant identification) to escape misunderstandingof long-read sequence data.[24]

High-quality phenotypic data

When examine connectionsbetween AMR genetic make-up and physical expression, it is crucial to utilize high-quality phenotypic data, using methods verified as perCLSI or EUCAST guidelines, to reduce mistake or variation (noise) in the Basic data because of the use of non-standard techniques. Minimum inhibitory concentration (MIC) dataare favored instead ofexplained (sensitive/moderate/Tolerant) data as the most detailed form of phenotypic AST data and can be re-evaluated when criticalpoints shift. Reference AST methods like liquid dilution method or solidmediumdilutionmethod (basedonthemicrobial andantibiotic) arepreferredothermethodsgenerating an MIC, such as gradient strip methods. Whereas other widely used methods such as Agar diffusion generate Numerical data (clear zones) intended to be changed to grouped results Understandings ("sensitive" or "Tolerant"), they are not directly

translatable into MICs, possibleReducing their value in the study of genetic-trait links, or lead findingof novel AMR processes when combined with genetic data. It must be mentioned even using the similar antibacterial and the sameisolates, various techniques can at times produce potentially crucialdifferences in MIC measurements.[25]

High-quality epidemiological metadata and appropriate sampling

Physical characteristics and DNA-related AMR results are oftencombined as monitoring data or research studies. These data areoften used to identify new problems requiring Preventing infection spread or health department action and guide such as treatment rules. To completely study and learn about AMR on a community level (instead of single person) level, collected data must be True sample of the group we want to study with little or no unfair collection, collected regularly Across different times and places. and may show too much serious cases and patients coming to hospital, Germs that don't respond to medicines, treatment not working, important groups, and sudden spread of disease, mainly in low-income and Systems where patient pays, and may lead to Guesses which are wrong or not true sample of the group we want to study.[26]

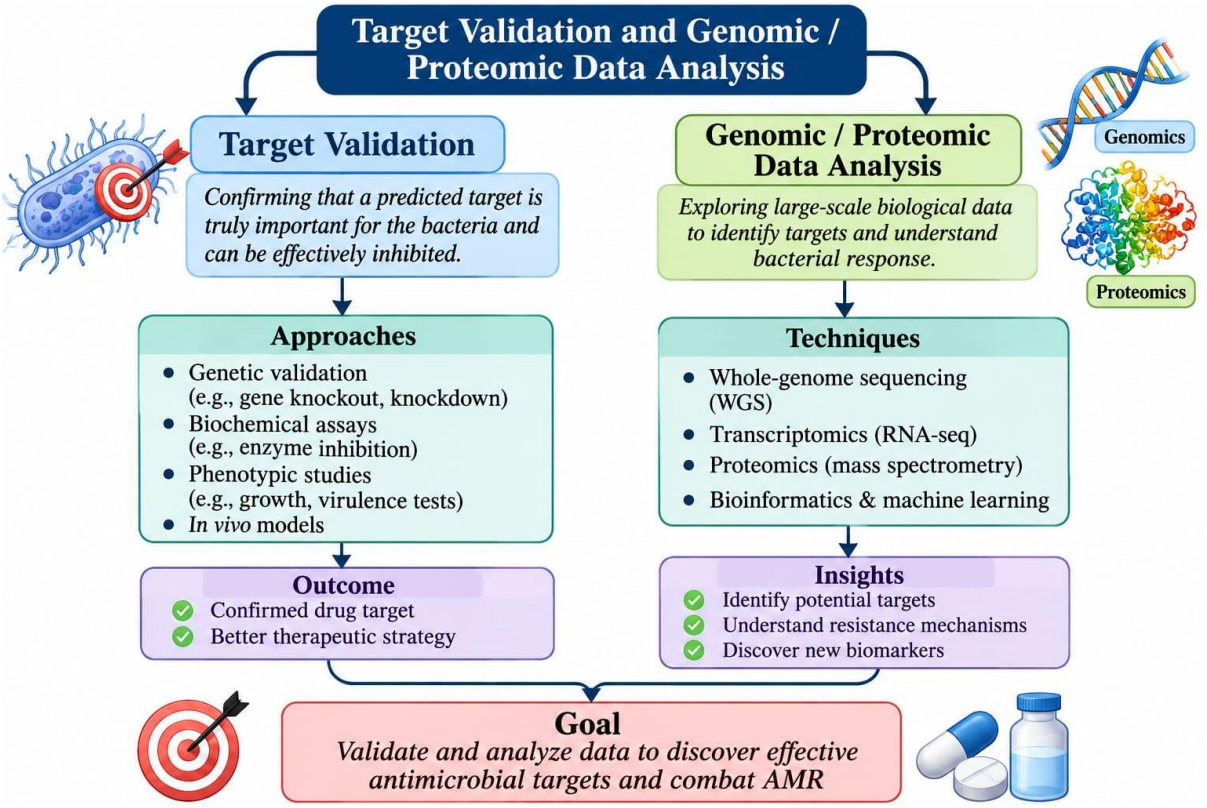

Figure 4: Target Validation and Genomic/Proteomic Data Analysis

DISCOVERY OF ANTIMICROBIAL AGENTS AND MOLECULAR DESIGN

For long time, antibacterial drugs have given cures for infectious diseases leading to efficient and successful therapy. Antibiotics have been known as antimicrobial agents and include any substance that inhibits the development of microbes such as microbes and fungi. several natural anti biotics have been made to heal many infections. The first was penicillin, detected in 1929. The best year antimicrobial research occurred during the 1940 to 1970 and cause to the treatment of f many bacterial/fungal diseases, although antibiotic tolerance quickly happened in microbes (Infectious Disease Society of America (IDSA) 2004). Immunity showed up in target organisms within a few years after the antibiotic was introduced into clinical use. This fact emphasizes the need for new antibiotic discovery (Demain and Spizek 2012). Within 7 years of penicillin's first use, one-half of Staphylococcus aureus samples developed resistant (Wenzel 2004). The resistance problem arises from heavy use of anti-bacterial drugs and thus rapid evolution of resistant bacterial strains. With an extremely rapid growth rate, bacteria and fungi can change genetically and become inherited resistant to antibiotics.[27]

New antibiotics discovered by 'classic' screening method

A number of agents that have been found by testing for bacterial killing microbes. Some of these, such

as fusidic acid, the pleuromutilins and lysostaphin, are not completely original but are listed here because of recent changes in their laboratory stage and clinical progress. Others on this list, including VIC 200107 and fidaxomicin are new agents.[28]

Modification of known antibiotics to enhance spectrum or improve safety

Lists a variety of antimicrobial agents currently under development that fall under the category of modification of known antimicrobials. Although this is a long list, it is not complete. It does, however, point out the fact that there still is a great deal of efforts going on in this arena. Moreover, it appears likely that many, if not the majority, of drugs listed in this table will finally be approved for patient use.[29]

Ceftobiprole and ceftaroline are the first anti-MRSA

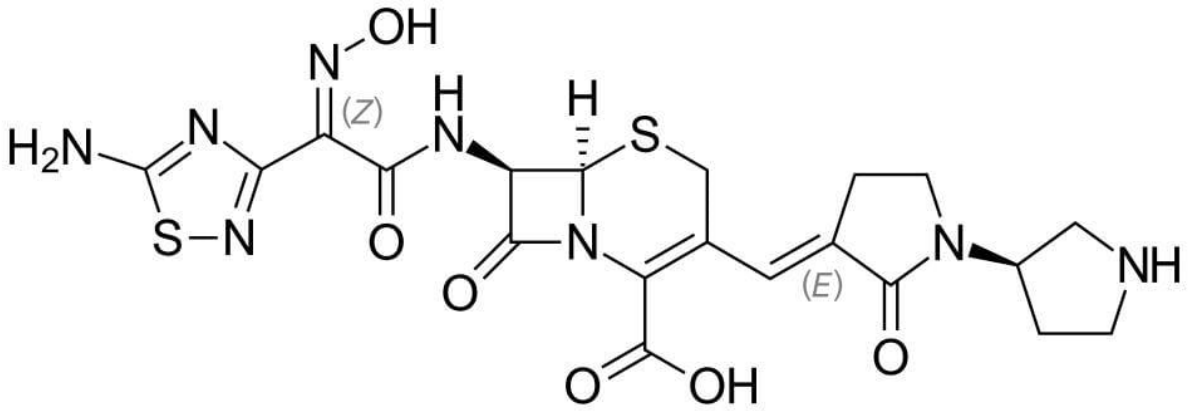

Figure 5: Ceftobiprole

Potentiation of activity of known compounds

The concept of the use of potentiators of known antimicrobial agents is almost as old as the antibiotic era. giving of antibiotic mixtures, in the hope of obtaining a combined or cooperative test, is the typical example of this method. However, despite innumerable in vitro studies showing increased potency of such mixtures against particular microbes, medical proof supporting use of combinations is restricted.[30]

Hybrid antimicrobial agents

The idea of chemical joining two antimicrobials or an antimicrobial agent with a boosting component has been the focus of research for many years. Initial research by Roche Laboratories and later by Procter & Gamble tested the potential utility of quinalactams, which are compounds resulting from the chemical linkage of cephalosporins and fluoroquinolones. Three chemical linkages are possible, namely ester, tertiary amine and carbamate. The esters were noted to act only.[31]

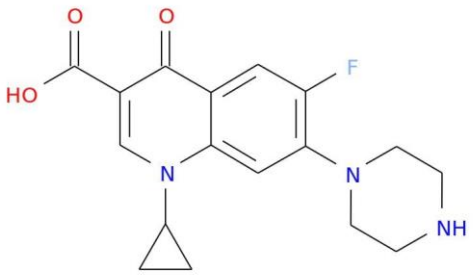

Figure 6: Ciprofloxacin

Peptides and related agents that target cellular membranes

There is currently much interest in creating new agents that attack the bacterial wall. Several natural

membrane-attacking peptides have been recognized and used in medicine since the 1950s, for about 70years including gramicidin, bacitracin and the polymyxins. Whole-body side effects, Body-wide harm Especially kidney damage has Restricted the use of these compounds to external use mostly, but the polymyxins (especially polymyxin E or colistin) have recently been brought back. (33)

Inhibitors of bacterial pathogenesis and/or virulence

At first glance, the processes by which bacteria stick to and enter human cells and the chemical process by which they make harmful poisons should be perfect targets for antimicrobial treatment and this is shown by a much research in these areas last many years. A number of methods to block bacterial binding have been Examined, such as: the use of small sugar chains that that host cell human cell sugar-protein and sugar-fats to which bacteria.(34)

New antimicrobial targets

Complete DNA mapping of many harmful bacteria has enabled to identify a many of vital genes that could of antimicrobial compounds. Combined with the accessibility of the human genetic sequence, this also increased the potential of directing against unique bacterial genes absent in humans or without considerable homology to human genes. However, so far, microbial genomics has failed to fulfill to this potential.(35)

AI-DRIVEN DRUG REPURPOSING FOR AMR

Concept of drug repurposing

Drug repurposing, also referred drug repositioning, includesdetecting novel therapeutic applications for availablelicenced or experimental molecules. For multidrug-resistance infections, repurposing presents animportant advantage by utilisingexisting pharmacological, tolerability, and preparation data to speed up clinical development, asopposed totraditional antibiotic discovery, which needs comprehensive preclinical and clinical assessment, repositioned drugs may avoid some initial-stage safety investigations, minimizing both drug development duration and expense.(36)

AI-driven drug repurposing refers to the application of data-basedcomputational methods that acquiremathematical or descriptive trends from data, specificallylabel guided and unlabelleddata-based machine learning (ML), deep learning (DL) incorporating graph neural networks (GNNs), and natural language processing (NLP) or knowledge-graph methods, to estimate or selectnovel antimicrobial applications for available licenced orexperimentalchemical substances.Molecularstructure-basedtechniques (Ligand target docking and molecular dynamics, MD), conventional quantitative structure–activity relationship (QSAR) simulation, and network-pharmacology evaluation are computer assisted but not inherently AI: they depend on physical-principle-based scoring, manually designedfeatures, or selectedassociationsystem instead of learned representations.(37)

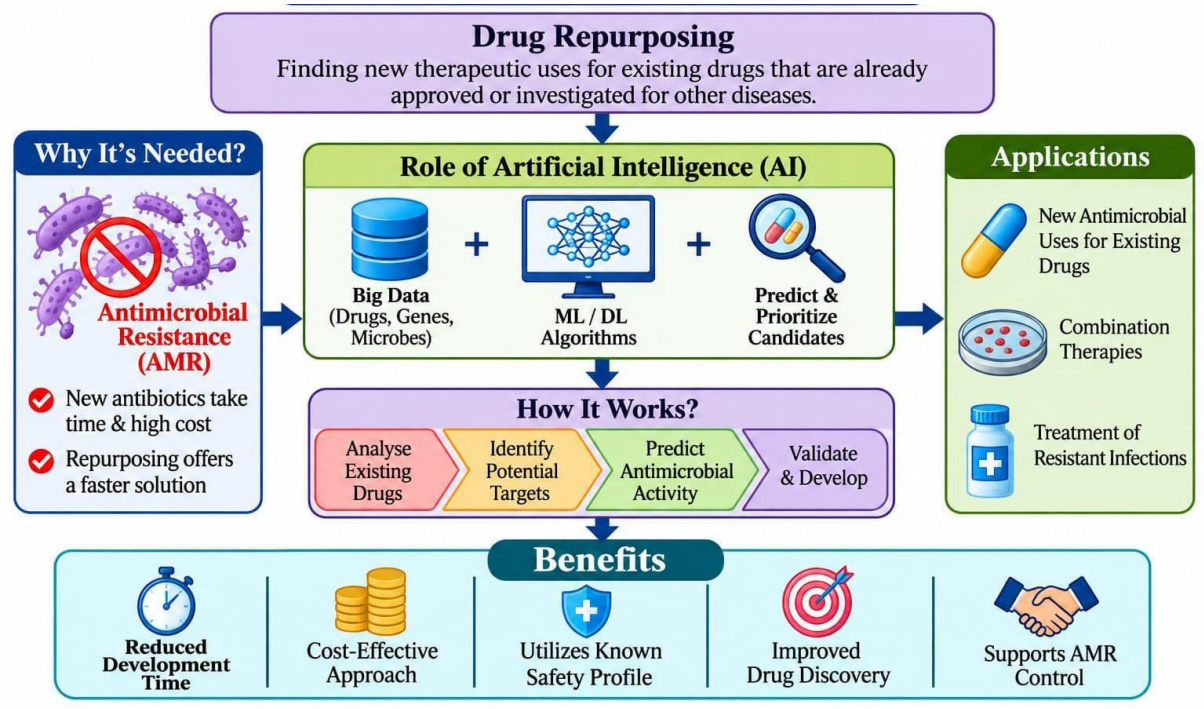

Figure 7: Drug Repurposing

IDENTIFICATION OF EXISTING DRUGS FOR NEW ANTI MICROBIAL USES

Repositioned drugs can function throughmultiple mechanisms, explained below.Direct anti-microbial action. Particular agentsshownatural bacteria killing or bacterial growth inhibitingactions towards MDR microorganisms; the antidiabetic candidate halicin, for example, such as a wide variety of Gram-negative and Gram-positive bacteria, such as carbapenem-resistant Enterobacteriaceae and M. tuberculosis in vitro and pan-resistant Acinetobacter baumannii in a mouse wound model, by reducing the ΔpH element of the proton motive force Host-modulation. theoretically, some repurposed drugs may improve host protection or regulate inflammatory signalling to promoteremoval of pathogens; for bacterial infections this mechanism is less well confirmed than direct or combined action and is not the main emphasis of the case studies below.Combined improvement of available antibiotics. Certain compounds without antibiotic properties can enhance antibacterial activity, such as by blockingdrug-export pumps and as aresultraisinginside cell antibiotic build-up; phenothiazines, firstdevelop as antipsychotic medications inhibit multiple-drug efflux-pump activity in Staphylococcus aureus. Efflux inhibition cannot, however, clarifyenhancement of β-lactams in general, because resistance to this class is caused mainly by β-lactamases and modified penicillin-binding proteinsSeveral translational challenges persist. Achieving effective drug level at infected tissues, especially for intracellular and biofilm-associated pathogens, is a key restriction. additionally, the pharmacokinetic (PK) and pharmacodynamic (PD) patterns of repurposed agents may be less effective for antimicrobial therapy, demandingdose adjustment or modification of drug formulation. Importantly, adjustmentexperimental preparation does not always convert intotherapeutic success because of host-microbe interaction's, toxicity, and off-target effects.AI-baseddrug repositioning approaches may help address some of these limitations by estimating compound efficacy, identifying combined drug interactions, and ranking candidates based on combined chemical, genomic, and phenotypic data. Network-oriented evaluations and multi-omics integration enable a systems-level understanding of drug–pathogen–host interactions, enhancing the possibility of successful translation. In sum, the principles of antimicrobial drug repurposing represent a combination between computational prediction and empirical validation that, by methodically utilising existing pharmacological knowledge while addressing PK/PD and mechanistic constraints, offers a possible faster route to the armamentarium against MDR pathogens.

Among topically applied medications, ciclopirox has antimicrobial activity. It suppressed the growth of *A. baumannii*, *E. coli*, and *K. pneumoniae*, irrespective any antimicrobial resistant of the strains. The possible mode of actionoccurs due to the potential blocking the production of LPS retain specific term in gram-negative microorganism, a component that shields bacteria against different compounds, including antibiotics. therefore, therapy could sensitize gram-negative bacteria to some classes of antibacterial drugs used in microbial diseases with Gram-positive bacteria (Brown, 2015). Ciclopirox is at present used only topically, but due to new possible therapeutic uses, such as in the treatment of cancer, investigations are ongoing on the potential for oral administration (Weir et al., 2011). Among the drugs used locally, zinc pyrithione, an antiseborrhoeiccompound, has showed bacteriostatic properties against streptococci and staphylococci. Its antimicrobial activity is thought to be related to the capacity to chelate metals and transport them through bacterial membranes (Saputo et al., 2018).

Ebselen is an organ seleniummolecule studied for its antioxidant, anti-inflammatory, and cell-protective properties (Maslanka and Mucha, 2023). This molecule displayed high antibacterial activity against strains of Gram-positive bacteria, including *S. aureus* resistant to methicillin, vancomycin, and linezolid. Additionally, it also increased survival in cases of sepsis in animal models. Ebselen also demonstrated activity against strains of vancomycin-resistant enterococci (VRE) and streptococci (Younis et al., 2015; Maslanka and Mucha, 2023). Ebselen also inhibited the production of toxins, α-hemolysin, and Panton-Valentine leucocidin, important virulence factors in the pathogenesis of *S. aureus*. It also reduced the survival of *S. aureus* and *E. faecium* bacterial cells in biofilms. When used topically, ebselen reduced the level of pro-inflammatory cytokines in skin infections caused by strains of *Staphylococcus*. It also showed synergistic activity in combination with many antibiotics, linezolid, clindamycin, vancomycin, chloramphenicol, erythromycin, rifampicin, and gentamicin (Maslanka and Mucha, 2023). The combination of ebselen with isoniazid could also bring good therapeutic effects also against antituberculosis drug-resistant strains of *M. tuberculosis* (Padiadpu et al., 2016; Sharma et al., 2023).

Ebselen reduces theenzyme related of thioredoxin reductase. This prevents bacteria from decreasing disulfides in molecules, which degrades DNA and protein synthesis and inducesoxidative damage inside bacterial cells (Maslanka and Mucha 2023). In gut infections ebselen also shields cells from

Clostridioides difficile toxins. These toxins damagegut epithelial cells and cause tissue damage. With ebselen treatment the gut microbiome heals better. The chance of repeated infections goes down (Bender et al., 2015; Garland et al., 2020).

Auranofin has become the focus of repositioning studies. This drug has been used for years to treat rheumatoid arthritis. Research shows that auranofin kills N. Gonorrhoeae strains. It does not affect normal lactic acid bacteria. Auranofin could fight the rising resistance seen in N. Gonorrhoeae to antibiotics. Importantly auranofin stops cells from releasing the pro-inflammatory cytokine IL-8 and provides a long-lasting post-antibiotic effect. Auranofin also kills MRSA, VRE and C. Difficile strains that cause colitis (Elkashif and Seleem 2020).

Auranofin shows action against gram-negative bacteria. This may happen because auranofin cannot cross the cell membrane. When auranofin is paired with colistin, a drug that makes membranes permeable the pair attacks gram- bacteria strongly even those that build biofilms such as P. Aeruginosa (Torres et al. 2018). The combination of colistin, ceftazidime and auranofin or colistin, rifabutin and auranofin also works well against isolates of K. Pneumoniae, A. Baumannii, P. Aeruginosa, C. Freundii, E. Cloacae and E. Coli that resist many drugs. Adding a drug to antibiotic regimens can help treat infections with multidrug-resistant strains. Auranofin also kills S. Pneumoniae strains that have MDR-type resistance (Sun et al. 2016).

Auranofin has recently earned orphan drug status from the FDA for treating amoebiasis in humans. This shows how drug repurposing can help fight infections (Younis et al., 2015). Auranofin was also studied for HIV-1 eradication (NCT02961829). Patients tolerated auranofin well when it was used with drugs and no serious side effects appeared in the study. Auranofin lowered the amount of DNA in blood cells shrinking the viral reservoir (Diaz et al. 2019). Researchers are also looking at auranofin as an add-on treatment, for lung cancer (NCT01737502) and giardiasis (NCT02736968).

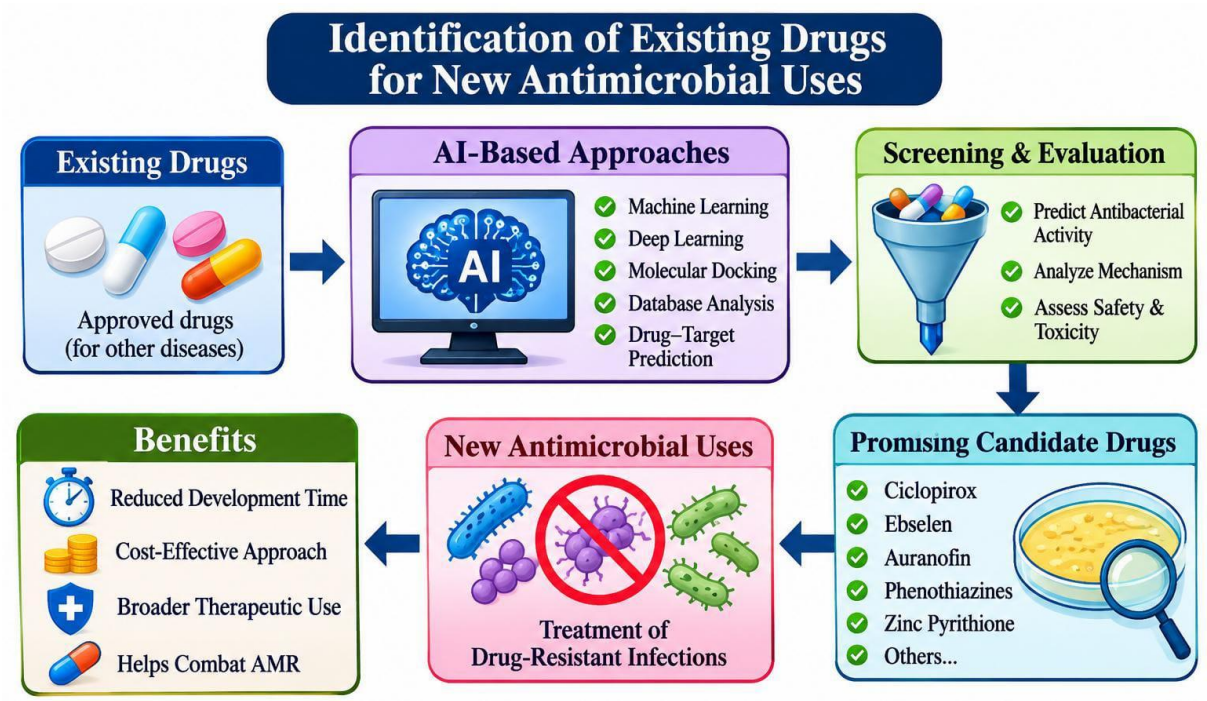

Figure 8:Identification of Existing Drugs for New Antimicrobial Uses

ADVANTAGES AND LIMITATIONS AND CASE STUDIES OF AI-DRIVEN DRUG REPURPOSING

Advantages

AI has revolutionized medicine. It is now a tool in almost every area of medical practice. It helps not in discovering new treatment methods but also in predicting how a disease might progress and in making accurate diagnoses. AI can even assist in monitoring a patient's signs and offer guidance on treatment steps during clinical assessments. This is especially true in drug development and drug repurposing where AI tools are very effective. They help in finding similarities between drugs and their targets or proteins. They also support generating treatment ideas and even creating new drugs from scratch. Finding similarities between molecules is a part of drug repurposing and many AI techniques are used to achieve this goal. Both the shape and the function of molecules are studied to find similarities. This is based on the idea that a drug tends to bind to molecules that're similar to known

ligands. In drug repurposing the focus is often on the structure of existing drugs to uncover uses. In contrast when creating drugs the attention shifts, to discovering new targets through protein amino acid sequence analysis. In this case representation learning methods can be applied. These are machine learning techniques that use unannotated data to learn features without human input.

Limitations

Despite making progress in the way we reuse drugs using computers there are still some big problems that stop this method from being used widely. One big issue is that the data comes from places and looks different. This can cause problems because the data might not be the same in ways. When we try to put types of data together it can be hard to make it all match up. This can sometimes hide biological information or create fake results. Some data is also. In some cases, more than a quarter of the important parts are not there. This makes it harder for the models to learn and make predictions. Another problem is that some models, the deep learning ones are hard to understand. They work like a box so it's not clear how they make decisions. Though using many models together can make them better it's hard to understand why they make certain predictions. Also, the models need to keep being checked because new information comes out all the time and the way we treat diseases changes. With careful checks the models can still be too focused, on the data they were trained on and not work well for new situations.

CASE STUDIES OF REPURPOSED ANTIMICROBIALS:THE ROLE OF AI AND LEVEL OF EVIDENCE

Not all repurposed antimicrobials discussed in the published studies were detected by AI. Halicin is a strong example of AI-based antibacterial discovery, whereas the antibacterial or synergistic properties of auranofin, phenothiazines, disulfiram, sertraline, and clofazimine were demonstrated through laboratory investigation or clinical observation, with computational methods playing at most a supplementary or historical role. Each case study below therefore states the role of AI clearly and the extent of computational, in vitro, animal, and clinical evidence.

1.Halicin (AI-Discovered)

Halicin, at firstexamined as a c-Jun N-terminal kinase suppressor for diabetes, was identified by a neural network model (a directed message-passing neural network) developed on prevention of proliferation data and utilised to the Drug Repurposing Hub. It inhibited the growth of a wide spectrum of bacterial microorganism in vitro, including M. tuberculosis and carbapenem-resistant Enterobacteriaceae, and was active in mouse models of pan-resistant A. baumannii wound infection and Clostridioides difficile infection. At the mechanistic level, it is reported to reduce the ΔpH component of the proton motive force, a mechanism distinct from that of most traditional antibiotics. The evidence is preclinical: therapeutic effectiveness data have not, to our knowledge, been reported, and the pharmacokinetic, toxicity, and formulation work required for systemic use remains to be finalised, underscoring the significance of combining AI forecasts with experimental pharmacology.

2.Auranofin (Antibacterial Activity Established Experimentally)

Auranofin, a gold-based compoundlicenced for rheumatoid arthritis, has antibacterial activity against Gram-positive bacteria such as MRSA and is suggested to function by interfering with thiol-redox homeostasis, including prevention of thioredoxin reductase. Its antibacterial action was shown experimentally; research in which AI-driven assessmentchosen auranofin antimicrobial could not be detected, and AI should not be attributed with its identification. Clinical developmentneeds pharmacokinetic and safety assessment at exposures relevant to antibacterial therapy, because the licenced dosing regimen was developed for another clinical application.

APPLICATIONS OF AI IN AMR DIAGNOSIS, SURVELLIANCE AND PRECISION MEDICINE

1.AI in diagnostics of AMR

Phenotypic and genotypic identification:Conventional bacterial grouping founded on phenotypic features has remained the main method which supports all later medical decisions in antimicrobial resistance control, such as therapy choice and infection prevention. though this method is commonly accessible, are like to suffer human mistakes and lengthy procedures whereas genotypic approaches provide higher accuracy but have been limited by expense and specialized skill. many studies show that machine intelligence, comprising automated learning and advanced neural learning, improves the correctness, ability to expand, and trustworthiness of infection examination in comparison to tradition hand-done methods in both phenotypic and genotypic bacterial identification and resistance profiling. Machine learning (ML) provided bacterial species-wise grouping by using computational models, for example the Support Vector Machine (SVM), Linear Regression, Decision Tree (DT), K-Nearest Neighbor (KNN), Neural Networks (NN), and Deep Learning (DL Bacterial growth tracking has also been handled by using artificial intelligence (AI) to help regular medical bacteriology lab processes. .44 created and tested a computer

program for automatic identification of bacterial development and early tracking within automated lab setup. The system was taught and tested using 3,844 culture plates obtained from a wide variety of patient samples and five standard culture media, with plates photographed multiple times at up to 15 incubation stages between 1 and 48 h. Importantly, the system found bacterial growth sooner than tradition human checking.

2.AI applications in AMR surveillance

AMR monitoring is the organized gathering, examination and sharing of antibiotic resistance information in different places/environment to assist government health rules and responsible antibiotic use. Conventional methods havelimitations in late reporting, scattered data whereas AI plays a changing role by allowing checking carrier, DNA based resistance mapping and studying trends in large groups combining of different types of data withinone Health structure. In monitoring processes, Artificial intelligence is often employed to recognize transmitters or sources by means of testing huge amounts of samples, or find tolerance from genetic data. A typical illustrative initial medical example is Hsu et al.,54 who created and confirmed an machine brain network to forecast the probability of MRSA presence employing many danger factors in a pair of hospitals, showing great correctness with true positive rate and specificity equilibrium that could help focused testing screening choices while complete monitoring is costly DNA based and metagenomic observation gives a supporting route in which AI helps understand the resistance potential of DNA- sequenced data. Arango-Argoty et al.49 introduced DeepARG, proposing deep learning models that use a distance matrix over ARG group to decrease wrong negatives results with closest match database method, and stating highly precise resistance types. To help surveillance strategy is newer predictive modelling goes beyond individual pathogens, but to cover broad susceptibility prediction of big bacterial and fungal groups. Mutisya & Kanguha51 stated decision tree-based ML (XGBoost) gaining high AUC for antibacterial and antifungal sensitivity prediction and emphasized its feasibility throughonlineinteractive toolsfor clinician support.Thelarge data driven AI-based examination has been proven to improve community-levelmonitoring bycombining heterogeneous datasets from country and global monitoring programs. Manik et al.68 showed that machine learning models applied to huge stores for example WHO GLASS and country health data can reveal local resistance directions and anticipate outbreaks. At the country policy level, AI surveillance has been incorporated to planning. Adekunle et al.69 applied machine learning procedures to many year monitoring data of bacteria, joining predictive analytics with modelling to evaluate the effect of stewardship programs and public awareness on AMR.

3.Precision medicine and clinical integration

Leading antimicrobial therapyis the clearest clinical application of sequence-driven precision medicine. WGS or mNGS can together detect species and find tolerance genes or genetic change, thus predicting antimicrobial sensibility. When provide within clinically actionable windows by conformed processes, genetic information can direct timely reduction of initial broad-spectrum therapy and the choice of target agent. The combining of sequencing with precision medicine redirects the method to infection control out of wide population-based approach to a treatment strategy kept for well-defined group determined by the pathogen genetic type, patient risk profile, and disease spread context. Fore casting indicator along with DNA sequences that are above one-pathogen identification, can also be produced during sequencing. Data about on pathogen families may inform the likelihood of therapy failure, return risk, or spread ability. Combination of pathogen genomics with host-response biomarkers (transcriptomics/proteomics) can enhance risk grouping and identify patients who could gain from adjunctive therapies.

CONCLUSION:

Antimicrobial resistance is a major global concern to worldwide public health. It highlights the immediate need it is to identify approaches to discover identify new antimicrobial agents and formulate improved therapeutic approaches. Artificial intelligence has become a tool in the fight against antimicrobial resistance. It helps in finding drug targets predicting how resistance happens and making sense of large amounts of genomic and proteomic data. Artificial intelligence also speeds up the search for antimicrobial compounds. Machine learning and deep learning are computer-based techniques. They can processbiomedical information and assist in identifyingpotential therapies that may be effective. AI can further be applied to repositionexisting medicines that are previously authorisedfor uses. This method can save time reduce costs and avoid some of the steps needed in traditional drug development. Examples like halicin, auranofin and ebselen show that old drugs can have antimicrobial effects against resistant bacteria. The quality of evidence varies and lab results do not always mean these drugs will work in humans. Still using intelligence in antimicrobial research has its limits. There are problems with data quality and consistency. Models sometimes are not easy to interpret. Predictions may not always be accurate. Toxicity is hard to

assess with AI. Turning a computational idea into a real treatment is often very difficult. That is why AI predictions mustbe followed up with lab experiments, animal studies and planned clinical trials. Then can we know if a treatment is safe and truly effective. In the end combining intelligence with microbiology, pharmaceutical sciences, genomics, proteomics and traditional drug development can lead to better antimicrobial therapies. Ongoing research, teamwork, across fields and solid experimental testing are key. These steps will help turn AI-based ideas into medicines. They will also help meet the growing threat of resistance.

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