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RESEARCH ARTICLE

THE APPLICATION OF ARTIFICIAL INTELLIGENCE IN ANTIBIOTIC DISCOVERY: AN OVERVIEW OF CURRENT AND FUTURE PERSPECTIVE

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Abstract

Innovative techniques for antibiotic discovery are required to hasten the development of effective therapies as the worldwide burden of antibiotic resistance rises. Artificial intelligence, a technological revolution in full swing, offers a hopeful future by removing bottlenecks in the pipeline for discovering new antibiotics. This review highlights how improvements in artificial intelligence are reviving the use of earlier antibiotic discovery approaches, including small molecule screening and natural product exploration. The use of modern machine learning techniques in new fields of antibiotic discovery, such as antibacterial systems biology, drug combination creation, antimicrobial peptide identification, and mechanism of action prediction, is then examined. Finally, we make a call to action for multidisciplinary collaboration and free access to high-quality screening datasets to hasten the development of novel antibiotic medications and the training of machine learning models.

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Introduction:-

Concerning levels of morbidity and mortality are being experienced worldwide due to antimicrobial resistance (AMR) in clinically significant bacteria[1]. Antibiotic-resistant bacteria are thought to be the source of 2.8 million infections in the US each year, 35,000 of which are fatal, according to the Centers for Disease Control and Prevention[2]. Since antibiotics have been found to significantly harm the gut microbiome, which reduces species diversity and promotes the evolution and spread of AMR genes, the current body of research also raises the possibility that the cure may be a component of the issue[3]. Clinically tested antibiotics are typically analogues of currently used medications for which AMR mechanisms have already been identified1, highlighting the need for new methods of antibiotic discovery[1].

The use of deep learning in antibiotic discovery has the potential to significantly advance the field of antimicrobial medicines[4].The use of antibiotics in modern medicine is crucial. However, the emergence of microorganisms resistant to antibiotics poses further difficulties for this paradigm in medical care. Antibiotic research and development must keep up with the microorganism resistance rate. Significant research has been done on new techniques for discovering antibiotics due to the arms race against pathogenic microorganisms. In a fast-growing area of this research, potential antibiotics are predicted in silico using a high throughput machine learning approach.

Historically, the discovery of antibiotics was based mainly on the search for secondary metabolites in soil-dwelling microbes that inhibited the growth of pathogenic bacteria[5,6]. Most antibiotic families currently used in medicine

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were developed using this method, including lactams, aminoglycosides, polymyxins, and glycopeptides. By boosting efficacy, lowering toxicity, and avoiding resistance-determining factors, semi-synthetic derivatives of these scaffolds have kept a therapeutic arsenal of antibiotics viable. Additionally, completely synthetic antibiotics from the pyrimidine, quinolone, oxazolidinone, and sulfa families have been clinically useful for a long time and are still being refined for the same characteristics.

This method resolves numerous issues with conventional discovery platforms and establishes a crucial standard for antibiotics in the future. We can win the arms race against pathogens resistant to antibiotics thanks to the increased efficiency offered by this technology and subsequent iterations.

Methodology:-

The goal of this review article was to present the role of artificial intelligence in antibiotic discovery and its perspective from the past twenty years, its present scenario, and its future applications. Thus, high-quality data that met the study objectives were included. In addition, comprehensive investigations on articles available in renowned databases like GoogleScholar, PubMed, Research Gate, and PMC articles were considered for literaturereview. The critical index words or phrases used during the literature search wereantibiotics, artificial intelligence, machine learning, drug discovery, antibiotic resistance, deep learning, antibiotic resistance, neural network and databases.

Inclusion criteria:
Scientific articles addressing the study objectives and written in English were included in the literature review.

Exclusion Criteria:
Studies published in languages other than English, literature thatdid not address the role of AI in antibiotic discovery, and literature dated before2000 were excluded.

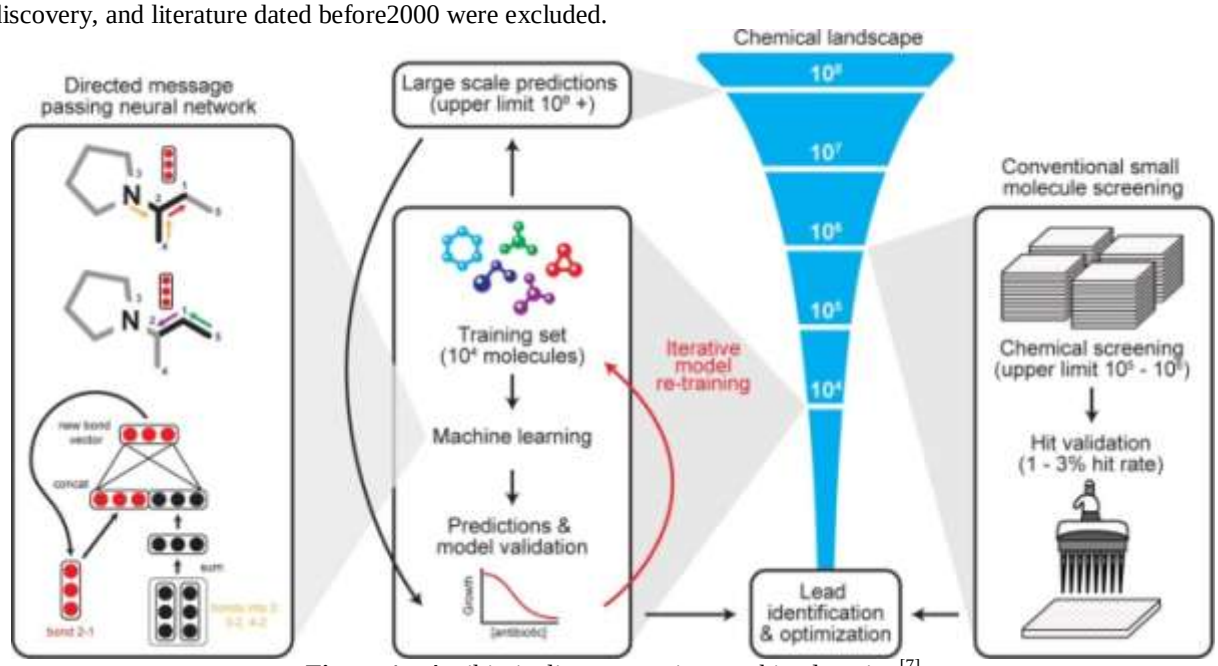

Figure 1:- Antibiotic discovery using machine learning[7]

Traditional discovery methods:
Traditional drug development methods are characterized by high prices, a lengthy synthesis, testing, and implementation time, expensive equipment, and significant human resources—possibly the toughest to come by. Drug research towards the pre-clinical and clinical testing phases can proceed more quickly thanks to automated computer-aided drug discovery processes that are both much less expensive and quicker.

The Waksman Platform is one of the earliest experimental platforms for antibiotic discovery. The Waksman Platform, first used by Rutgers microbiologist Selman Waksman, involved screening soil-borne actinomycetes on a field of overlaying bacteria[8]. Antibiotics are frequently produced by actinomycetes in the soil environment.

Candidate antibiotic-producing bacteria were primarily found when a zone of inhibition on the plate formed. Using this method, numerous significant antibiotics, including streptomycin, were successfully found. Although this platform was crucial in discovering many antibiotics used today, it has some drawbacks. First, the number of soil antibiotics is limited. Methods to examine a broader range of soils and bacterial habitats have largely failed to create novel antibiotic classes[9]. Second, the method is challenging to scale up, making the procedure time-consuming and difficult. These are only a few factors that have led to the development of high-throughput computational methods for antibiotic discovery.

The initial step in the conventional workflow for discovering antibiotics is the isolation of the producers (such as actinomycetes) from various environments. To semi-select the microorganisms, soil samples are primarily isolated and streaked with serial dilutions on certain solid media. Following a morphological inspection of the plates, promising candidates (such as colonies resembling actinomycetes) are selected and multiplied, often utilizing various mediums to examine the isolates' potential for biosynthetic production. Agar diffusion assays are used to evaluate extracts, culture supernatants, and agar with the mycelium for actinomycetes.

Machine learning and deep learning:

Artificial intelligence in medicinal chemistry can predict the efficacy and toxicity of possible therapeutic molecules. ML algorithms can spot patterns and trends that human researchers would miss, making it possible to propose new bioactive substances with fewer side effects more quickly than traditional protocols. Recent training of a DL algorithm employing a dataset of known medicinal molecules and their associated biological activity has resulted in major contributions to toxicity prevention, as has been described[10,11].

In addition to searching through a huge amount of data and choosing compounds that fit the necessary criteria, machine learning can be used to forecast and discover novel antibiotics. Parvaiz et al. [12] extensive search for compounds with the property of beta-lactamase inhibition was made possible by machine learning. 74 compounds out of the 700,000 listed compounds were found and given empirical confirmation. Seven substances were classified as class C beta-Lactamase CMY-10 inhibitors, whereas eleven were classified as CMY-10 enhancers. Twenty-eight more substances were discovered, all of which showed antibacterial properties.

Antimicrobial resistance has been brought on by the COVID-19 pandemic's numerous secondary infections brought on by bacteria that are multidrug resistant. The use of artificial intelligence techniques like machine learning and deep learning may make it possible to deliver potential antibiotic candidates more quickly. The challenge of antibiotic discovery should be evaluated using both empirical and contemporary methods and technologies in a cogent, thorough, and effective manner.

AI has been used to find new cancer-fighting drugs, including MEK, BACE1, and COVID-19. Large databases of possible chemicals have been analyzed using machine learning algorithms to determine which has the best chance of curing the virus. In other instances, these AI-driven methodologies have identified interesting medication candidates in a fraction of the time it would take using conventional techniques.

A review of deep learning (DL) models used to predict drug-target interactions (DTI) and the development of novel medications was presented by Kim et al. in 2021[13]. They noted a few barriers to the promising future of de novo drug development and DL-based DTI prediction. However, they failed to consider the most recent developments in DL application for DTIs, including XAI and DTs.

Virtual Screening (VS) ML applications were presented by Rifaioglu et al. [14],including methodology, tools, datasets, and resources. They showed examples of VS research that led to the discovery of novel bioactive compounds and treatments while highlighting DL technologies available as open-source programming libraries. In their literature evaluation, they did not consider drug dose optimization.

High-throughput Fourier-transform infrared spectroscopy was used by Da Cunha et al. [15]. to combine machine learning, spectroscopy, and the mechanisms of action and efficacy of antibiotics. This method was able to quantify antibiotic potency by looking at metabolic fingerprints and accurately predict the many antibiotics in the same class's modes of action.

A review of feature-based chemogenomic techniques for DTIs prediction was presented by Sachdev and Gupta in 2019[16]. In addition to pertinent datasets, techniques for figuring out drug or target features, and evaluation measures, they offered a current summary of the various methodology, datasets, tools, and measurements. The most recent DL application for DTIs should have been considered.

In their analysis and search of the Roche compound library, Zoffman et al. [17]. Employed machine learning to prioritize compounds based on their novelty, potency, chemical makeup, and accessibility as pure powder materials. To measure the antibacterial activity of these substances, four Gram-negative bacteria were used as test subjects. Machine learning was used to recognize and gather the diverse bacterial phenotypic fingerprints concerning various compounds' varied modes of action to understand better the relationship between the structure and activity of specific antibacterial medications.

Neural networks and antimicrobial compounds:

Neural network models were recently employed to construct a novel representation and evaluate the antibacterial potential of previously discovered pharmaceuticals that were repurposed as antibiotics. Multiple copies of a model are combined using the ensemble learning technique, which weighs the input from each model to arrive at the final prediction. It has been applied to various tasks, from the discovery of proinflammatory peptides to the foretelling of adverse medication reactions.

Deep neural networks and support vector machines (SVMs), two traditional ML methods, have been utilized to describe AMPs and calculate associated MOAs. In order to predict peptide activity against P. aeruginosa, researchers in 2009 compiled 44 peptide characteristics and fed them into an artificial neural network. The 20 natural amino acids were converted into pseudo residue types using a deep convolutional neural network model developed in a study from 2020 using a condensed amino acid vocabulary. For the genome-based prediction of the lowest inhibitory doses of 20 antibiotics against Klebsiella pneumoniae and 15 antibiotics against nontyphoidal Salmonella bacteria, extreme gradient boosting was applied. Regression models, input representations, and RNNs were developed to choose peptide sequences with antibacterial activity. Peptide sequences were also embedded in a latent space[18–20]

Fully Connected Neural Networks are identified using multi-layer perceptrons, which transform two-digit data inputs into linear and nonlinear functions. This model works best for classification and regression challenges with real-valued data since it incorporates the Sigmoid Curve, Hyperbolic Tangent, and Rectified Linear Unit as three representations for nonlinear functions[21].

A sophisticated and high-potential ANN variation called the classic convolutional neural network (CNN) model was created to handle increasing complexity levels and data pretreatment and compilation. It can be processed through four phases: one input layer, two output layers, and a sampling layer. It is based on how the neurons in an animal's visual brain are structured. One or more connected layers in CNNs connect the sample and output layers[22].

To extract, examine, and evaluate the peptides of the sea anemone Cnidopus japonicas and their antimicrobial properties, Grafkaia et al. [23]. They have conducted a transcriptome investigation. They created a search strategy using in silico machine learning to find toxin-like proteins that contained antimicrobial peptides. Ten peptides were chosen and produced. Three of them—peptides A1, A3, and B1—executed antimicrobial activity in the following way: one was active against both Gram-positive and Gram-negative bacteria, but the other two only reduced the growth of Gram-positive bacteria. The potassium-channel inhibitory toxin identified in Stichodactylahelianthus is comparable in chemical structure to the peptide A1, which has an alpha-helix and amino acid strand. The presumptive structure of peptide B3 revealed a similarity with GsMTx2, a toxin produced by the tarantula Grammostolaspatulate that blocks mechanosensitive ion channels. Antimicrobial peptides can effectively combat a variety of multidrug-resistant bacterial strains, and the introduction and advancement of machine learning and other AI technologies can further aid research in this area.

To discriminate between bacteriocin and non-bacteriocin sequences, Hamid et al. [24]. used a Recurrent Neural Network (RNN) and a word-embedding representation for each trigram from a protein sequence. Compared to existing AI-based algorithms, the results indicated that their RNN-based system was the most effective automated approach for categorizing bacteriocins.

In order to forecast phenotypic polymyxin resistance (PR) in Klebsiella pneumoniae clonal group 258, Macesic et al. applied machine learning. Their methodology included a reference-based strategy (which made use of variant calling and insertion sequence identification) with a reference-free strategy (which made use of the detection of k-mers). Utilizing a reference-based and carefully curated input data set led to the best results. The approach can be enhanced by filtering bacterial genome-wide association study (GWAS) data and combining clinical information on antibiotic exposure [25].

When treating carbapenem-resistant Acinetobacter baumannii with antibiotic combinations, Smith et al. applied machine-learning approaches to optimize dose regimens. To more accurately represent the drugs' intrinsic activity and efficacy, they added mechanism-based models to the pharmacodynamics data. The strategy was unidirectional based on evidence from literature models and polymyxin B's effects on meropenem. The study produced six improved antibiotic combination treatment regimens that could increase the likelihood of eradicating microorganisms in 50 to 90% of the simulated patients. However, the combination would require doses higher than those permitted and/or advised by the recommendations. Rigorous monitoring techniques were also employed to keep this combination effective for some individuals [26].

Combining a machine learning method with multiple conformational high-throughput docking to find inhibitors of YpkAa key virulence factor affecting host actin cytoskeletal rearrangements and phagocytosis. Hu et al. suggested a multifaceted strategy to combat Yersinia species' antibiotic resistance. After the machine learning model was developed, resulting in an accuracy of 70%, and combining the method with virtual screening, 45 compounds were chosen to be experimentally examined for inhibitory characteristics. Of these 45 compounds, seven were able to stop the growth. This shows how machine learning may be used to find new substances having antibacterial activity[27].

Economic impact:

DiMasi et al. examined the R&D expenditures for 106 new medications randomly chosen from 10 pharmaceutical firms. In 2013, the average cost of a newly approved compound—including post-approval and research and development expenses—was $2870 million[28]. A new medicine entering the market had an average likelihood of 11.83%. In contrast to the 30–40 antibacterial drugs that are now in research, some 4,000 immuno-oncology medicines are[29]; this is because antibiotics are less expensive than other, more expensive treatments, are used for shorter periods than chronic treatments, and have usage restrictions to prevent misuse.

Antibiotic-resistant bacterial infections are becoming more prevalent in the US due to the widespread use of conventional antibiotics, leading to diverse drug-resistant strains. Antibiotic-resistant bacteria affected 2.9 million people in 2013, leading to 23,000 annual fatalities. Twelve thousand eight hundred persons lost their lives as a result of the 223,900 instances of Clostridioides difficile infections that were documented in the USA in 2017[30]. More than $4.6 billion was estimated by Nelson et al. [31]. to have been spent on treating community- and hospital-onset infections in 2017.

The SWOT study by Miethke et al. [32], Provides a particular viewpoint on creating innovative antibiotic medications, stressing the potential benefits and long-term solutions of emerging artificial intelligence technology. The widespread use of antibiotics in animals and the emergence of multidrug-resistant bacteria pose a danger to the effectiveness of antibiotics, necessitating the development of novel antibiotics with faster entry into clinical usage and more specific methods of action.

Future opportunities and strategies:

As discussed above, other machine learning platforms have solved many problems with the Waksman Platform and other comparable systems. Machine learning strategies can significantly increase the rate of antibiotic discovery when compared to manually screening soil-derived microorganisms and their potential antibiotics. Analysis in silico is used to accelerate processing time. The finding rate will probably increase as computers become more effective over time. Increased drug libraries and better learning algorithms will also play a significant role in raising the discovery rate.

This strategy will be less expensive as a computer process takes the role of physical tools and human resources. With the deep learning model, predictions that previously might have required several microbiologists and years can be made in a matter of days. Additionally, this method is not constrained by the source of the candidate compounds. The Stokes et al. [7]., 2020 method examines more structurally varied chemicals from numerous sources, in contrast

to the Waksman platform's reliance on finding distinct soil-borne, antibiotic-producing actinomycetes. Over 750 million compounds are present in the ZINC15 database used in this machine-learning method.

Drug Repurposing Hub, halicin, exhibits bactericidal action against a broad phylogenetic spectrum of pathogens, including Mycobacterium TB and carbapenem-resistant Enterobacteriaceae, and differs structurally from traditional antibiotics. In murine models, salicin also successfully cured infections caused by pan-resistant Acinetobacter baumannii and Clostridioides difficile. Additionally, among a discrete group of 23 empirically validated predictions from >107 million molecules filtered from the ZINC15 database, our model found eight antibacterial agents that are structurally different from well-known antibiotics.

Emerging technologies associated with Industry 4.0 enable the development of digital twins (DTs), which are digital representations of actual entities that communicate with the original through dynamic, two-way communications. Although DTs are employed in many other industries, they have not yet been fully integrated into the production of pharmaceuticals. In today's cutthroat markets, new digital technologies are necessary to foster innovation, boost efficiency, and boost profitability. Industry 4.0 is a theory put forth by the professional community to raise automation levels and improve productivity and efficiency at work.

The constant advancement of AI technology has created new opportunities for drug creation and given us the means to combat microorganisms resistant to antibiotics effectively. The "antibiotic crisis", as it is currently being called, is caused by a lack of antimicrobial agents and rising drug resistance. The difficulties currently experienced by patients and healthcare professionals must be overcome, which calls for increased collaboration between academic institutions and the drug-development industry. A viable method in that AI technology can positively impact the pharmaceutical and healthcare sectors is through creative approaches that quicken and reduce the cost of drug development.

Conclusion:-

The use of modern machine learning techniques in new fields of antibiotic discovery, such as antibacterial systems biology, drug combination creation, antimicrobial peptide identification, and mechanism of action prediction, needs to be studied in further detail. Action for multidisciplinary collaboration and free access to high-quality screening datasets to hasten the development of novel antibiotic medications and the training of machine learning models is required.

References:-

1. De Oliveira DM, Forde BM, Kidd TJ, Harris PN, Schembri MA, Beatson SA, et al. Antimicrobial resistance in ESKAPE pathogens. ClinMicrobiol Rev 2020;33(3):e00181-19.
2. CDC. Antibiotic Resistance Threats in the United States, 2019. Technical Report (US Department of Health and Human Services; CDC, 2019).
3. Chng KR, Ghosh TS, Tan YH, Nandi T, Lee IR, Ng AHQ, et al. Metagenome-wide association analysis identifies microbial determinants of post-antibiotic ecological recovery in the gut. Nat EcolEvol 2020;4(9):1256–67.
4. Shankarnarayan SA, Guthrie JD, Charlebois DA, Shankarnarayan SA, Guthrie JD, Charlebois DA. Machine Learning for Antimicrobial Resistance Research and Drug Development [Internet]. IntechOpen; 2022 [cited 2023 Feb 16]. Available from: https://www.intechopen.com/chapters/81918
5. Wright GD. Opportunities for natural products in 21st-century antibiotic discovery. Nat Prod Rep 2017;34(7):694–701.
6. Clardy J, Fischbach MA, Walsh CT. New antibiotics from natural bacterial products. Nat Biotechnol 2006;24(12):1541–50.
7. Stokes JM, Yang K, Swanson K, Jin W, Cubillos-Ruiz A, Donghia NM, et al. A Deep Learning Approach to Antibiotic Discovery. Cell 2020;180(4):688-702.e13.
8. Selman Waksman and Antibiotics - Landmark [Internet]. Am. Chem. Soc. [cited 2023 Feb 16]; Available from: https://www.acs.org/education/whatischemistry/landmarks/selmanwaksman.html
9. Valiquette L, Laupland KB. Digging for new solutions. Can J Infect Dis Med Microbiol 2015;26(6):289–90.
10. Hansen, K. et al. Machine learning predictions of molecular properties: Accurate many-body potentials and nonlocality in chemical space. J. Phys. Chem. Lett. 6, 2326– 2331 (2015).

11. Pérez Santín, E. et al. Toxicity prediction based on artificial intelligence: A multidisciplinary overview. Wiley Interdisciplinary Reviews: Computational Molecular Science vol. 11 e1516 (2021).
12. Parvaiz N, Ahmad F, Yu W, MacKerell Jr AD, Azam SS. Discovery of beta-lactamase CMY-10 inhibitors for combination therapy against multidrug-resistant Enterobacteriaceae. PLoS One 2021;16(1):e0244967.
13. Kim J, Park S, Min D, Kim W. Comprehensive survey of recent drug discovery using deep learning. Int J Mol Sci 2021;22(18):9983.
14. Rifaioglu AS, Atas H, Martin MJ, Cetin-Atalay R, Atalay V, Doğan T. Recent applications of deep learning and machine intelligence on in silico drug discovery: methods, tools and databases. BriefBioinform 2019;20(5):1878–912.
15. Ribeiro da Cunha B, Fonseca LP, Calado CR. Simultaneous elucidation of antibiotic mechanism of action and potency with high-throughput Fourier-transform infrared (FTIR) spectroscopy and machine learning. ApplMicrobiolBiotechnol2021;105:1269–86.
16. Sachdev K, Gupta MK. A comprehensive review of feature-based methods for drug target interaction prediction. J Biomed Inform 2019;93:103159.
17. Zoffmann S, Vercruysse M, Benmansour F, Maunz A, Wolf L, Blum Marti R, et al. Machine learning-powered antibiotics phenotypic drug discovery. Sci Rep 2019;9(1):5013.
18. Nguyen M, Brettin T, Long S, Musser JM, Olsen RJ, Olson R, et al. Developing an in silico minimum inhibitory concentration panel test for Klebsiella pneumonia. Sci Rep 2018;8(1):1–11.
19. Yan J, Bhadra P, Li A, Sethiya P, Qin L, Tai HK, et al. Deep-AmPEP30: Improve short antimicrobial peptides prediction with deep learning. MolTher-Nucleic Acids 2020;20:882–94.
20. Nguyen M, Long SW, McDermott PF, Olsen RJ, Olson R, Stevens RL, et al. Using machine learning to predict antimicrobial MICs and associated genomic features for nontyphoidal Salmonella. J ClinMicrobiol 2019;57(2):e01260-18.
21. Mukhamediev RI, Symagulov A, Kuchin Y, Yakunin K, Yelis M. From classical machine learning to deep neural networks: a simplified scientometric review. Appl Sci 2021;11(12):5541.
22. Yamashita R, Nishio M, Do RKG, Togashi K. Convolutional neural networks: an overview and application in radiology. Insights Imaging 2018;9:611–29.
23. Grafskaia EN, Polina NF, Babenko VV, Kharlampieva DD, Bobrovsky PA, Manuvera VA, et al. Discovery of novel antimicrobial peptides: A transcriptomic study of the sea anemone Cnidopus japonicus. J BioinformComputBiol 2018;16(02):1840006.
24. Hamid MN, Friedberg I. Identifying antimicrobial peptides using word embedding with deep recurrent neural networks. Bioinformatics 2019;35(12):2009–16.
25. Macesic N, Bear Don't Walk OJ, Pe'er I, Tatonetti NP, Peleg AY, Uhlemann AC. Predicting Phenotypic Polymyxin Resistance in Klebsiella pneumoniae through Machine Learning Analysis of Genomic Data. mSystems 2020;5(3):e00656-19.
26. Smith NM, Lenhard JR, Boissonneault KR, Landersdorfer CB, Bulitta JB, Holden PN, et al. Using machinelearning to optimizeantibioticcombinations: dosingstrategies for meropenem and polymyxin B againstcarbapenem-resistantAcinetobacterbaumannii. ClinMicrobiolInfect 2020;26(9):1207–13.
27. Hu X, Prehna G, Stebbins CE. Targetingplaguevirulence factors: a combinedmachinelearningmethod and multiple conformational virtual screening for the discovery of Yersinia protein kinase A inhibitors. J Med Chem 2007;50(17):3980–3.
28. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceuticalindustry: new estimates of R&D costs. J Health Econ2016;47:20–33.
29. Yu JX, Hubbard-Lucey VM, Tang J. Immuno-oncology drug developmentgoes global. Nat Rev Drug Discov 2019;18(12):899–900.
30. Centers for Diseases Control and Prevention, Threat Report. [(accessed on 11 October 2021)];2013 Available online: https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
31. Nelson RE, Hatfield KM, Wolford H, Samore MH, Scott RD, Reddy SC, et al. National estimates of healthcare costs associated with multidrug-resistant bacterial infections among hospitalized patients in the United States. Clin Infect Dis 2021;72(Supplement_1):S17–26.
32. Miethke M, Pieroni M, Weber T, Brönstrup M, Hammann P, Halby L, et al. Towards the sustainable discovery and development of new antibiotics. Nat Rev Chem 2021;5(10):726–49.