Review Article

Role of AI (Artificial Intelligence) Driven Synthesis of Antimicrobial Peptide (AMP) as a Potential Antibacterial Agent Against Multi-Drug Resistance (MDR) Pathogens - A Narrative Review

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ABSTRACT

Antimicrobial peptide (AMP) is a small type of protein that has many antibacterial effects. In recent days antibiotic resistance is a serious problem Antibiotics alone cannot kill bacteria so combinatorial therapy shows some hope for eradicating bacterial resistance. The natural AMP shows less activity against bacteria rather synthetic AMP. In the meantime, scientists observed that AI-based AMPs are more effective than others. Various tools were introduced to synthesize AMP of our own choice like we can choose which AMP targets which sites This review specifically focuses on how different tools can synthesize various types of AMP, how they can be advantageous, some examples of AI-driven AMP that are in clinical trials and lastly how they can be a great hope for eradication of bacterial resistance.

Keywords: Artificial intelligence, antimicrobial peptide, multi-drug resistance bacteria, machine learning.

INTRODUCTION

One of the most significant contemporary public health issues is the well-known presence of multidrug-resistant (MDR) microorganisms. Nosocomial infections are typically linked to MDR microorganisms. Some MDR bacteria, however, are now common sources of illnesses that are acquired in the community. This result is significant because the spread of MDR bacteria in communities increases the number of people at risk, which in turn increases the number of MDR bacterial illnesses.

Almost all antibiotics now on the market have been found to exhibit a variety of bacterial resistance mechanisms. Utilizing medications with advantageous pharmacokinetic characteristics that allow for quick entry to the intended target site is crucial, as evidenced by the correlation between the length of antibiotic exposure and the emergence of antibiotic resistance. Combinational therapy, which combines two or more antibiotics according to their susceptibility pattern so that the two agents can work synergistically, is one way to increase the susceptibility of bacteria to conventional antibiotics. This strategy is advantageous because it can elicit an enhanced response [1].

Collaboration between pharmaceutical specialists and AI researchers is essential to the creation of novel and potent medicines for a range of illnesses. Numerous drug discovery processes, such as chemical compound identification, target identification, peptide synthesis, drug toxicity and physiochemical property assessment, drug monitoring, drug efficacy, and effectiveness assessment, bioactive agent prediction, protein-protein interaction, protein folding and misfolding identification, structure and ligand-based virtual screening (LBVS), QSAR modelling, and drug repositioning, are now possible thanks to computational modelling based on AI and ML [2]. Through AI the synergistic effect of AMP and antibiotics can be detected nowadays [3].

Mechanism of Action of AMP:

Since AMPs primarily target microbial membranes, it is more difficult for bacteria to become resistant to AMPs than it is to traditional antibiotics. Three models—the barrel-stave model, the toroidal-pore model, and the carpet model—have been put forth to describe how AMPs permeabilize bacterial membranes [4].

AMPs can interact with elements of bacterial membranes because of their positive net charge, leading to cell death and the rupture of the lipidic bilayer. As suggested by Gazit and associates in 1996, AMPs can also disintegrate parallel to the membrane, totally encasing it and simultaneously creating micelles with the initial ruptured membranes (carpet model) [4].

Despite the fact that the chemical structure of LPS varies among bacteria, defensins have the ability to neutralize it in various bacteria. LPS Because it is amphiphilic, it can self-aggregate and form oligomers at a Critical Micelle Concentration (CMC), which is the concentration of LPS or any other surfactant at which it aggregates in micelles [5].

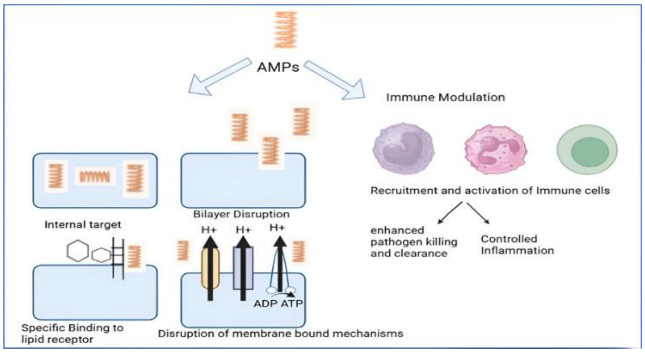

Figure 1: Mechanism of action of AMP created with Bio Render

Challenges in AMP Development:

A recent study that examined the existing literature indicates that various databases can be inferred as among that AMPs are among the most appealing research fields for scholarly interest with significant potential within the realm of pharmaceuticals. Although there is great potential and interest, only a limited number of AMPs have received FDA approval for clinical application. It is widely recognized that the process of discovering and developing drugs is intricate, and lengthy, and consists of multiple stages: target identification and discovery, selection and design for enhancement, preclinical and clinical evaluation, and approval. The exact mechanism of action remains unclear, and this factor is crucial for creating peptides with enhanced activity and reduced toxicity [6].

The expense of AMPs is quite substantial because of the larger count of amino acids. The size of an AMP may influence its capacity to target and permeate microbial membranes, as longer peptides demonstrate a broader spectrum of activity against a diverse array of microorganisms. Generally, at least 7 to 8 amino acids are needed for an amphiphilic arrangement. Moreover, a minimum of 22 amino acids is necessary for an αhelix configuration that can traverse the bacterial lipid bilayer, while just 8 amino acids suffice for βsheet AMPs. Consequently, acquiring peptide medications at affordable production costs is challenging, primarily because of low synthesis yields and intricate purification processes [6].

The stability and minimal antibacterial effectiveness of AMPs pose further difficulties for these peptides. AMPs can be degraded by proteases and are affected by serum components, salts, and variations in ph. The ionic strength of the solution can influence the electrostatic interaction between peptides and the bacterial membrane. Moreover, elevated levels of salts, like those present in physiological saline solutions, may impact the stability and effectiveness of AMPs. Salt ions may engage with charged amino acid residues in AMPs, altering their structure and possibly influencing their antimicrobial function. Moreover, salt and hydrophobic characteristics can influence the solubility and aggregation features of AMPs 6.

Environmental pH is another factor that can have a significant impact on the stability and activity of AMPs. Most AMPs show optimal antimicrobial activity at neutral or slightly acidic pH levels, which are typical of many body tissues. For example, the pKa of histidine is about 6.5, and clavanin A, a histidine-rich peptide, has a high net positive charge at pH 5.5 and is relatively lightly charged at pH 7.4, which affects the antibacterial activity. However, extreme pH conditions, such as highly acidic environments in the stomach or alkaline conditions in the intestine, can affect the structure and function of AMP [6].

The possible cytotoxic effects of AMPs on humans are another concern that must be considered in preclinical and clinical research. Overall, AMPs exhibit lower toxicity to mammalian cells relative to numerous traditional antibiotics. Nonetheless, their possible toxicity may differ based on various factors, such as peptide sequence, concentration, method of administration, and target cell type. Depending on their mode of action, AMPs may induce toxicity by either attaching to a receptor or interacting with the membrane. Receptor peptides influence the immune system by exhibiting bacteriostatic effects. Elevated levels of AMP can lead to other secondary inflammatory conditions like rosacea, atopic dermatitis, or psoriasis due to unchecked or excessive immune reactions. Peptides that form pores, like melittin, exhibit a lytic impact, including on human cells, characterized by nonspecific toxicity. The application of this peptide in safe doses shows no antibacterial effectiveness. Melittin is still undergoing clinical phase I trials. Hydrophobicity serves as another crucial element for antimicrobial effectiveness, aiding the incorporation of AMPs into microbial membranes. Nonetheless, a peptide that is excessively hydrophobic may also harm mammalian cells, resulting in toxicity and a reduction in selectivity towards microbial cells.

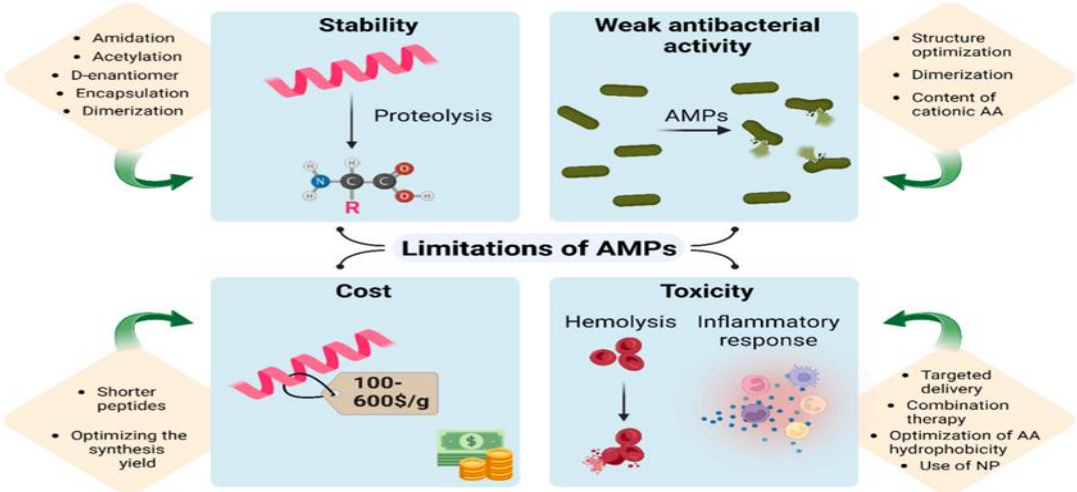

Figure 2: Limitations of drug-resistant AMPs and strategies to tackle these limitations: stability, weak antibacterial activity, toxicity, and cost.

To reduce the possible toxicity linked to excessive hydrophobicity, one approach is to balance the hydrophobic and hydrophilic residues of AMP to attain optimal antimicrobial effectiveness against pathogens while lessening toxicity to mammalian cells. Drug carriers, required to possess two key characteristics—absence of cytotoxicity and immunogenicity—can facilitate the delivery of AMP while minimizing toxicity to host cells. Nanotechnology-driven delivery systems and the encapsulation of AMP within liposomes or nanoparticles show great promise for enhancing stability and minimizing toxicity as a result of their small size, increased surface area, and targeted site delivery. The method of delivering the medication can affect the toxicity characteristics of AMP [6].

AI-Driven Synthesis of Antimicrobial Peptides

- Role of AI in AMP discovery:

The Proper Roles of AI in the Discovery of AMPs are-

Discrimination and Generation: It assists in the discovery of potential AMPs and the creation of new peptides. Discriminators estimate important characteristics such as activity and toxicity, while generators propose new AMPs, or simply new peptides in the case of de novo generation or analogues of known peptides[7].

Machine Learning Models: These models include the use of ML models to estimate and design AMP through the analysis of sequence-based features. These models assist in the development of optimal peptide libraries and the study of chemical space of the AMP(8) Predictive models have been developed to target specific pathogens like those listed by the World Health Organization with high accuracy [9].

Deep Learning and Encoding Methods: Deep learning models employed in AI4AMP use physicochemical property-based encoding to predict the antimicrobial potential with very high accuracy as compared to conventional methods [10].

3D Structural Analysis: Three-dimensional structural characteristics of AMPs are still being explored by AI-driven approaches to design peptides with more than one antimicrobial mechanism [11].

Case Studies of AI-designed AMPs Enhanced Properties:

Designing Novel AMPs: AMPs have great potential as next-generation antimicrobial agents, but their clinical use faces challenges such as low stability, high toxicity, haemolytic effects, and susceptibility to proteolytic degradation [1,2,3]. Research is actively addressing these issues to improve AMP performance. Designing effective AMPs involves selecting suitable amino acid sequences, optimizing physicochemical properties, and assessing antimicrobial activity [4]. Their cationic nature, due to positively charged residues like lysine and arginine, enhances the electrostatic attraction to microbial membranes, leading to bacterial cell disruption [5]. Optimizing these properties can improve selectivity and therapeutic potential.

Rational design: Chemical alteration of antimicrobial peptides:

Rational design involves utilizing structural and bioinformatic tools to identify the most effective amino acid sequences and physicochemical characteristics for targeting specific microorganisms. This approach may involve chemically modifying existing peptide sequences or developing new peptide mimetics (peptidomimetics) that resemble known peptides in both structure and function. Typically, rational design prioritizes key factors such as amino acid composition, sequence length, hydrophobicity, net positive charge, secondary structure, and amphiphilicity, as explored in various studies [6].

Amino acid substitution: Modifying AMPs' properties, such as hydrophobicity, amphipathicity, sequence length, and charge, can greatly influence their activity 7. Since only a few key amino acids contribute to their antimicrobial function, other residues can be altered or removed with minimal effect. Substituting amino acids changes physicochemical traits like net charge and hydrophobicity, impacting potency. For example, while human cathelicidin consists of 37 residues, only the C-terminal segment (residues 17–29) is responsible for its antimicrobial activity and has inspired potent peptide variants [8,9].

Modifying specific amino acid residues within the FK13 region of the LL-37 peptide has led to the development of multiple analogues with strong antimicrobial activity against multidrug-resistant pathogens, such as MRSA and vancomycin-resistant *Enterococcus faecium* (VREF) [9]. Likewise, de Breij et al. (2018), the KR-12 peptide, created by substituting Phe at the 17th position of LL-37, demonstrates potent antimicrobial effects against *Escherichia coli* while maintaining low toxicity to animal cells. Various other LL-37 variants have exhibited significant antimicrobial, antibiofilm, anticancer, and wound-healing properties. For instance, researchers synthesized several analogues by randomly substituting amino acids in the C-terminal chain of LL-37, among which SAAP-148 displayed exceptional antimicrobial activity in the micromolar range against antibiotic-resistant bacteria such as MRSA and multidrug-resistant *Acinetobacter baumannii*. Additionally, SAAP-148 has shown strong antibiofilm effects, the ability to eradicate persister cells, and promising wound-healing properties in ex vivo studies.

Naturally occurring antimicrobial peptides (AMPs) typically carry a positive charge ranging from +2 to +13 [10]. Modifying their overall net charge by substituting cationic amino acid residues can influence their interaction and binding affinity with negatively charged microbial membranes, thereby affecting their antimicrobial effectiveness [11,12]. For instance, increasing the positive charge of aurein 1.2 (GLFDIIKKIAESF-NH2), a short yet highly potent peptide derived from the skin of the *Litoria aurea* frog significantly enhances its antibacterial properties 9. Similarly, aurein M2, which has a net charge of +5 due to the substitution of Glu 11 and Asp 4 in aurein 1.2, exhibits greater antibacterial activity against P. aeruginosa, S. aureus, and E. coli than its parent peptide, which has a net charge of +1 9. However, while raising the cationic charge of AMPs can improve their antimicrobial

potency, exceeding a certain limit may lead to increased toxicity.

Capping (terminal/side chain modification): Post-translational modifications are widely used in peptide-drug engineering. Natural AMPs like cathelicidins, defensins, and aureins often have C-terminal amidation (–NH2), which supports their structural stability and antimicrobial function [13]. Their secondary structure plays a key role in interactions with microbial membranes .

Common techniques for capping antimicrobial peptides (AMPs) include C-terminal modification (amidation) and N-terminal modifications such as acetylation, methylation, and lipidation [14,15]. These modifications enhance the structural stability of AMPs, protect them from enzymatic degradation, and help maintain or improve their antimicrobial effectiveness.

C-terminal amidation involves converting the peptide's carboxyl (-COOH) group into a carboxamide (-CONH2) by substituting the hydroxyl group with a nitrogen atom. This modification can be carried out through chemical or enzymatic methods and has been shown to improve stability while reducing toxicity [16]. For instance, aurein 2.5 with a C-terminal carboxyl-amide modification (GLFDIVKKVVGAFGSL-CONH2) exhibits greater antimicrobial activity against *K. pneumoniae* compared to its carboxylated counterpart (GLFDIVKKVVGAFGSL-COOH) [17].

The increased efficacy of amidated peptides is attributed to their enhanced conformational stability. For example, modelin-5-CONH2, the carboxyl-amidated version of modelin-5, demonstrates improved helical stability and stronger antimicrobial action against *E. coli* than its non-amidated counterpart, modelin-5-COOH [17].

Halogenation: Halogenation is a powerful strategy for enhancing the properties of bioactive compounds, including AMPs. This process incorporates halogen atoms like chlorine, fluorine, bromine, or iodine to optimize drug performance. Compared to other amino acid substitutions, halogenation is more effective, with over a third of clinical trial drugs utilizing this modification [18, 19].

Fluorination, the incorporation of fluorine atoms, is widely utilized to improve the pharmacokinetic properties of antimicrobial agents. Many drugs, both those currently under clinical investigation and those already approved for use—such as Ciprobay (ciprofloxacin, an antibacterial agent), Lipitor (a cholesterol-lowering medication), and Prozac (an antidepressant)—contain fluorine ions [20]. The ability of fluorine to modify the electrostatic characteristics of bioactive compounds makes it a valuable tool for drug enhancement. Importantly, fluorine can influence the conformational structure of peptides containing aliphatic halogenated amino acids, which in turn affects their pharmacological properties, including increased resistance to proteolytic degradation [21, 22].

Halogenation significantly alters the properties of antimicrobial peptides (AMPs), resulting in greater stability, improved solubility, and enhanced antimicrobial activity, even under challenging physiological conditions. This modification increases their effectiveness against target pathogens [23]. A notable example is the halogenation of jelleine-I, a short AMP derived from the venom of the royal jelly of honeybees (*Apis mellifera*), which substantially improves its therapeutic potential[24]. Replacing phenylalanine with its halogenated analog leads to a remarkable enhancement in the antibacterial and antibiofilm activities of peptide derivatives, along with improved stability [24]. Additionally, Jia et al. (2023) reported that halogenated jelling-I derivatives demonstrate strong efficacy against bacterial-associated colorectal cancer (CRC), surpassing the widely used antibiotic metronidazole. These findings underscore halogenation as a powerful approach for increasing the potency of therapeutic agents.

Conjugation with nanoparticles: Nanotechnology is an advancing field focused on creating and manipulating nanoparticles for applications in science, engineering, and medicine. In nanomedicine, the integration of nanotechnology with drugs enhances pharmacological properties such as stability, targeted delivery, and cellular uptake [25,26]. Various nanoparticles, including ceramics, carbon-based, lipid-based, and semiconductor types, are increasingly used to optimize antimicrobial peptides (AMPs) [26, 27]. Embedding AMPs into nanoparticles boosts their stability and antimicrobial efficacy. This integration follows two key approaches: passive delivery, where peptides are encapsulated without surface modifications, and direct delivery, which involves conjugating AMPs to surface-modified nanoparticles for precise targeting [28].

Other nanoparticles, such as polymeric nanoparticles like poly(lactic-co-glycolic acid) (PLGA) and magnetic nanoparticles, have also been integrated into antimicrobial peptides (AMPs). PLGA is widely recognized for its low toxicity, excellent biocompatibility, and ability to provide controlled and sustained drug release, making it a highly effective drug delivery system [29]. For instance, the development of Smart PLGA-Based Nanocrystal Carriers (SGNCs) loaded with gliclazide, a Biopharmaceutics Classification System (BCS) Class II drug used to manage type 2 diabetes mellitus, successfully addressed drug delivery and therapeutic limitations [30]. This formulation significantly enhanced gliclazide's solubility, dissolution rate, and bioavailability in a type 2 diabetes rat model compared to the pure drug.

De Novo Design: De novo design leverages computational tools, including AI and ML, to generate novel antimicrobial peptide (AMP) sequences with specific traits. By analyzing amino acid preferences, composition, and frequency, researchers can design diverse sequences with varying structures and functions. Understanding the physicochemical properties and structure-activity relationships of AMPs allows for predictive modeling and optimization of peptides with desired antimicrobial properties [31].

Cutting-edge technologies, especially AI, have revolutionized drug discovery by accelerating the design of antimicrobial peptides (AMPs). AI-powered screening analyses millions of peptide sequences, identifying functional motifs and predicting antimicrobial activity based on physicochemical properties. Machine learning models, trained on large AMP datasets, enable the rapid design of highly effective novel peptides [32,33].

The "quantitative structure-activity relationship" (QSAR) machine learning model, which utilizes physicochemical descriptors to assess the pharmacological potential of peptides, has emerged as an essential tool in the design of effective antimicrobial agents 34. By analyzing chemical attributes like electrostatic charge and molecular weight, QSAR can predict a compound's biological activity or toxicity based on its molecular structure, as well as assist in identifying promising lead compounds for drug development. [35]

Table 1: AI-Designed Antimicrobial Peptides in Preclinical and Clinical Development

Peptide/Project	AI Approach	Target Pathogens	Development Stage	References
AMP-Designer Peptides	Foundation model integrating contrastive prompt tuning, knowledge distillation, and reinforcement learning.	Broad-spectrum Gram-negative bacteria	Preclinical (in vitro and in vivo validation)	12
SCUB1-SKE25 & SCUB3-MLP22	AI mining of human proteome to identify cryptic antimicrobial peptides	Drug-resistant bacteria	Preclinical (mouse models)	12
AMP-24 & AMP-29	Generative AI pipeline with classification filtering	Bacterial and fungal pathogens	Preclinical (mouse infection models)	13
Ani AMP pred	AI-guided discovery from animal genomes	Various pathogens	Preclinical (computational predictions)	14

Potential Applications against MDR Pathogens:

In Vitro and In Vivo Efficacy of AI Designed: -AI-designed antimicrobial peptides (AMPs) have demonstrated significant potential in combating multidrug-resistant (MDR) bacteria. Leveraging advanced methodologies like multimodal variational autoencoders (VAEs) and deep learning, these peptides are tailored to exhibit enhanced antimicrobial properties 15. For example, the M3-CAD pipeline efficiently generates AMPs targeting six major MDR pathogens. These peptides are designed with broad-spectrum activity, reduced toxicity, and increased stability, streamlining the discovery process compared to conventional methods [16].

Peptides such as AIG-R5, developed through AI, have shown remarkable efficacy against challenging pathogens like colistin- and carbapenem-resistant *Acinetobacter baumannii*. Notably, AIG-R5 disrupts biofilms effectively, reducing pre-formed biofilms by 60%, while synergizing with antibiotics like aminoglycosides to enhance their efficacy 16. This dual action combines biofilm eradication and antibiotic potentiation, all while maintaining minimal toxicity.

AI-generated AMPs are also potent against both Gram-positive and Gram-negative MDR bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus epidermidis 17*. By targeting bacterial membranes—a mechanism less prone to resistance development—they provide a versatile solution for diverse infections. However, challenges such as limited in vivo stability and potential toxicity persist. Current engineering efforts focus on optimizing hydrophobicity, cationic charge, and membrane selectivity to address these issues and improve therapeutic outcomes [18].

Limitations of AI-driven AMP Synthesis:

Data Limitations: -AMP datasets often exhibit a disproportionate representation of peptides originating from specific species, regions, or experimental settings. This imbalance hinders predictive models from effectively generalizing across diverse biological environments, limiting their reliability when addressing underrepresented groups or scenarios. Consequently, models trained on such skewed datasets frequently underperform in predicting the activity of AMPs derived from rare organisms or unique environmental conditions. This is particularly concerning in identifying effective responses to novel or diverse pathogens. Furthermore, limited diversity in training data restricts models' ability to adapt to new, real-world data—a significant drawback in fields like personalized medicine and global health [36]. Developing high-quality, diverse AMP datasets poses significant challenges, such as high costs, technical barriers, and a reliance on established knowledge repositories that often prioritize well-researched species or domains.

Complexity of Host-Pathogen Interactions: Antimicrobial peptides (AMPs) have gained attention as potential alternatives to conventional antibiotics because of their broad-spectrum effectiveness and lower likelihood of promoting resistance [37]. Nonetheless, anticipating their interactions within intricate biological systems continues to be a major obstacle.

Table 2: Computer-designed AMPs in terms of antibacterial potential

Computer-aided design	Peptide name	Target bacteria	Resistant antibiotics	References
QSAR	XPF, XPF10a^{N} DRAMP02272a DRAMP02273a X1-20a^{*,N} CPF-P2, CPF-P2a^{N} CPF-P3, CPF-P3-(10a^{N}, 12a^{N}, 20a^{N}) CPF-MW1, CPF-MW-(10a^{N}, 12a^{N}, 20a^{N}) PS-PB-(8a^{N}, 14a^{N}, 16a^{N}, 20a^{N}) Opis (8a^{N}, 16a^{N}) AamAP1, AamAP-S1, AamAP-S1a^{N}, AamAP1-lys, AamAP1-lys-a^{N} A3, A3a^{N} K3-IsCTa K7P8K11-IsCTa A1F5K8-IsCTa Os*, Os-a^{*,N}, Os-C, Os(3-12), Os(11-22)a* W3(Os-C) a, W3(Os-C) a^{N} OmDefB^{*,N}, OmDefB19^{N} W-OmC-Ca, W-OmB-Ca^{N} ThetaDefA^{*,U}, ThetaDefB^{*,U} BTD11a^{*,N}, BTD15a^{*,N} CP, DP, Mapcon AP HDPs	*E. coli NCTC12923* *E. coli LEC001* *P. aeruginosa PA01* *P. aeruginosa NCTC13437* *A. baumannii ATCC17978* *A. baumannii AYE* *K. pneumoniae M6* *K. pneumoniae NCTC13368* *S. aureus ATCC9144* *S. aureus NCTC13616* *S. aureus USA300* *S. aureus 1199B* *C. parapsilosis NCPF3209* *C. tropicalis NCPF8760* *E. coli ATCC25922* *A. baumannii ATCC19606* *B. subtilis ATCC6633* *E. faecalis ATCC29212* *S. aureus ATCC6538* *S. aureus ATCC25923* *E. coli ATCC25726* *E. coli ATCC25922* *P. aeruginosa ATCC27853*	Ceftazidin Ciprofloxacin Doxycycline Gentamycin Colistin Imipenem Fluconazole Rhizocticin Amikacin Biochanin A Erythromycin	19–23
De Novo	Arp (1-3) SP15D E (1-3) H (1-3)	*E. coli K-12 BW25113* *S. typhimurium LT2* *E. coli MG1655* *S. aureus ATCC2523* *E. coli ATCC25922*	Kanamycin Streptomycin Protamine Amoxicillin Tetracyclin Enrofloxacin Methicillin Gentamycin Amikacin Biochanin A	24–28
Linguistic model	OP_145, Omiganan, Syphaxin, Alacemycin, Centaxin, Killixin, Sophieganan, Suselkan, Armaganan, Ratigan	*S. aureus ATCC33591* *E. coli ATCC25922* *E. coli ATCC43827* *A. baumannii ATCC BAA1605* *P. aeruginosa ATCC9027*	Methicillin Oxacillin Penicillin Cephalosporin Biochanin A Carbapenem Aminoglycoside Fluoroquinolones Ampicillin	24–27
Pattern insertion algorithm	AMP_ (1-3), HP1404 GMG_05Z, GMG_01_SCR, GMG_03 A 13-mer peptide Temporin-Ali	*S. epidermidis ATCC29886TM* *S. aureus ATCC33591* *P. aeruginosa ATCC27853* *E. coli MG1655*	Vancomycin Methicillin Oxacillin Cephalosporin Carbapenem Kanamycin Chloramphenicol	29–32
Evolutionary algorithm	LBD_{MJ}, LBD_{B}, LBD_{A-D}, LBD_{X}, LBD_{Y}, pGFP	*Vibrio parahemolytics* *Vibrio harveyi* *Vibrio alginolyticus* *Vibrio owensii* *Photobacterium damselae* *E. coli* *Staphylococcus epidermis* *Staphylococcus aureus* *Kurthia gibsonii*	Ampicillin Cephazolin Tetracycline Streptomycin Erythromycin Sulphonamides Fluoroquinolones Penicillin Methicillin	33–35

Biological membranes are intricate assemblies consisting of diverse lipids, proteins, and carbohydrates, with their composition varying widely across different cell types and organisms [38]. This variability poses challenges for accurately simulating membrane interactions with antimicrobial peptides (AMPs) using simplified lipid bilayer models [39,40].

Membranes are highly dynamic structures that continuously fluctuate and undergo phase transitions [41]. These dynamic characteristics can affect the binding and function of AMPs, making accurate predictions difficult [42].

Antimicrobial peptides (AMPs) can induce various cellular responses, such as disrupting membranes, forming pores, and interacting with intracellular targets 43. These effects are often multifaceted and involve numerous signaling pathways, which complicates the prediction of an AMP's overall impact on a cell.

Molecular dynamics simulations, widely used to explore biomolecular interactions, depend on force fields to define a system's potential energy. However, existing force fields often struggle to accurately represent the intricate interactions between antimicrobial peptides (AMPs) and biological membranes, particularly when accounting for variables such as membrane curvature and lipid diversity [42].

Although in vitro studies offer valuable insights into AMP-membrane interactions, they may not fully capture the complexity of biological systems. In vivo studies are crucial for evaluating the overall efficacy and potential toxicity of AMPs; however, interpreting their results can be challenging due to the many factors that affect drug delivery and distribution [42].

High-throughput screening techniques are valuable for identifying potential antimicrobial peptide (AMP) candidates, but they frequently utilize simplified assays that may not fully reflect the diverse activities of AMPs. The limited availability of detailed experimental data on AMP interactions with membranes presents a significant challenge to developing precise predictive models [42].

Clinical Translation Challenges: -The incorporation of artificial intelligence (AI) across diverse domains, including drug discovery, holds transformative potential for advancing the development of novel therapeutics. In the specific area of antimicrobial peptides (AMPs), AI-driven approaches present a compelling solution to the escalating issue of antibiotic resistance. Nevertheless, the pathway to regulatory approval, clinical trial implementation, and successful commercialization of AI-designed AMPs entails distinct challenges. This review examines the existing knowledge on these topics and highlights critical considerations surrounding the regulatory frameworks, clinical evaluation processes, and market strategies for these cutting-edge therapies [43].

Regulatory approval**:** AI-designed antimicrobial peptides (AMPs) represent a new category of therapeutics, presenting unique challenges for regulatory agencies that are more accustomed to conventional drug development processes. These agencies may require comprehensive information about the AI algorithms used in the design, including details about their training datasets, validation procedures, and performance metrics. Achieving transparency and explainability in AI models is essential for gaining regulatory approval, necessitating clear explanations of how the AI system generates its design outcomes. Additionally, rigorous preclinical and clinical testing is critical to establish the safety and efficacy of these AI-designed AMPs, with all studies conducted in compliance with existing regulatory standards and guidelines [44].

Clinical trials: Selecting suitable patient populations for clinical trials is a challenging task, particularly for innovative treatments such as AI-designed antimicrobial peptides (AMPs). Establishing appropriate endpoints for these trials necessitates a thorough evaluation of the unique characteristics and mechanisms of action of AI-developed AMPs. Ethical aspects, including ensuring informed consent and safeguarding data privacy, are crucial in studies involving AI-driven therapeutics. Additionally, AI-enabled adaptive trial designs present opportunities to streamline clinical trial processes and expedite drug development [44].

Commercialization: Safeguarding intellectual property rights for AI algorithms and AMP designs is vital for achieving commercial success. Developing reliable manufacturing processes and establishing efficient supply chains for AI-generated AMPs poses distinct challenges. Addressing regulatory barriers and obtaining reimbursement for AI-designed AMPs can be a complex and lengthy process. Furthermore, raising awareness among healthcare providers and patients about the advantages and possible risks associated with AI-designed AMPs is crucial for ensuring their broader acceptance [45].

Future Perspective:

Advances in AI algorithms for drug discovery: Future developments in AI techniques including deep learning and reinforcement learning are

expected to significantly improve antimicrobial PAM design. Current AI models, such as generative adversarial networks (GANs) and other machine learning algorithms, have already shown promise in generating novel PAMs with potent antibacterial activity against multidrug-resistant (MDR) pathogens [46,47]. Continued advances in these AI algorithms are likely to improve the accuracy and efficiency of PAM design, enabling the discovery of peptides with optimized properties to combat MDR bacteria.

Personalized Antimicrobial Peptides: The potential of AI to design personalized AMPs based on pathogen- or patient-specific data is a promising future direction. Personalized medicine approaches can use AI to tailor AMPs to the specific resistance mechanisms and infection profiles of each patient or pathogen. This can lead to more effective treatments with reduced side effects, as AI can predict and design peptides that are highly specific for target bacteria while minimizing toxicity to human cells [46,48,49].

Integrating AI with other technologies: AI can integrate with other emerging technologies such as CRISPR, nanotechnology, and microbiome studies to improve the efficacy of PMAs. For example, AI-designed PMAs can be combined with CRISPR-based gene editing tools to target and disrupt bacterial resistance genes, or with nanotechnology to improve the delivery and stability of PMAs in the human body [49,50]. In addition, it understands the role of the microbiome in the human body. Health and disease can help design PMAs that selectively target pathogenic bacteria while preserving beneficial microbiota[50].

Overcoming regulatory and commercialization barriers: Bringing AI-designed PMAs to market faster requires strategies to overcome regulatory and

commercialization barriers. This includes demonstrating the safety and efficacy of these peptides through rigorous preclinical and clinical testing, as well as developing scalable and efficient manufacturing processes. Collaboration between AI researchers, biotechnologists, regulators, and pharmaceutical companies will be key to addressing these challenges and ensuring that AI-designed AMPs can reach patients in need [48,49,50].

In summary, the future of AI-guided antimicrobial peptide synthesis holds great promise for addressing the growing threat of multidrug-resistant pathogens. Advances in AI algorithms, custom design of AMPs, integration with other technologies, and overcoming regulatory hurdles are key areas driving the development and application of these new antibacterial agents. Taking advantage of these advances, we can hope to develop more effective treatments. Effective and targeted at multi-resistant infections, improving patient outcomes and public health.

CONCLUSION

AI-driven AMP synthesis is a new direction in the research field. As AMP has much efficacy in killing bacteria and in decreasing infections, AI-driven AMP synthesis is a very good approach to make AMP more proficient and more effective against bacteria. By AI different AMPs can be designed for our desirable choices. In the future, AI-driven Amp will show more variation in their structure, their mechanism, etc.

So, we can conclude that AI-driven AMP synthesis will give a promising result in the future and advancement should be done in the process of forming AMP through Artificial Intelligence. Advances in AI algorithms, custom design of AMPs, integration with other technologies, and overcoming regulatory hurdles are key areas driving the development and application of these new antibacterial agents. Taking advantage of these advances, we can hope to develop more effective treatments. Effective and targeted at multi-resistant infections, improving patient outcomes and public health.

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