Deciphering the Key Properties for Overcoming Bacterium-induced Drug Resistance and Potentiating Anti-cancer Immune Response

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Abstract. Antimicrobial and cancer resistance represent two of the most significant global health challenges nowadays, with growing evidence suggesting interconnections between bacterial infections and cancer progression. There is an urgent need for innovative strategies that synthesically incorporate biological information and computational methodologies. This study aims to implement machine learning (ML) and deep learning (DL) models to predict antimicrobial peptides (AMPs) with anticancer potential. This approach leverages positive and negative datasets retrieved from public databases to build comprehensive models, establishing a *in silico* framework to predict the anticancer activity of antimicrobial peptides as well as their antimicrobial properties, paving the way for novel investigations into the dual therapeutic potential of these peptides in infectious disease treatment and cancer therapy.

Keywords: Antimicrobial Resistance, Drug Discovery, Antimicrobial Peptides, Machine Learning

1 Introduction

1.1 Context and Motivation

The increase in antimicrobial and anticancer drug resistance poses a major public health threat, leading to a loss of effectiveness of current treatments [1]. Nowadays, the current global landscape is slightly different from the past because drug resistant pathogens and the connection between bacterial infections and cancer progression have significantly undermined traditional treatments and increased mortality rates. It is now more challenging than ever to introduce an effective antibiotic to the market considering the rapid emergence of antimicrobial resistance (AMR), which exceeds the rate of antibiotic drug discovery. According to the European Centre for Disease Prevention and Control [2], in the EU, 25000 people die annually due to infections caused by resistant bacteria. 10 million deaths per year are projected between the years 2015 and 2050 if current infection and resistance problems are not reversed. Hence, new approaches must be developed to accelerate the rate of drug discovery process and meet the current demand for new antibiotics [3]. Since recent advances in computational power and analysis of extensive biological datasets, ML protocols are significantly impacting the prediction of AMR patterns, serving as 'the bridge' between *in silico* predictions and clinical applications [4], creating unprecedented opportunities to develop treatments that can simultaneously combat bacterial infections while improving anticancer responses, offering hope for overcoming one of the most pressing public health challenges of our time.

1.2 Objectives

The primary objective of this project is to develop computational tools to understand the key properties that make antimicrobial peptides overcome bacteria-induced drug resistance while boosting anticancer immune responses. The project will first focus on assembling and curating comprehensive datasets of antimicrobial peptides, and subsequently a range of conventional machine learning and deep learning models will be considered and the one with the best predictive performance will be selected. In short, finding a model capable of predicting the dual activity of the given candidates in the datasets.

2 Contextual Explanation

2.1 Antimicrobial Resistance

The overuse and misuse of antibiotics in clinical settings have accelerated resistance development in pathogenic microorganisms. Effective treatments are becoming increasingly obsolete, and common infections are more difficult and more expensive to treat. A key concern is the emergence of multidrug resistant pathogens, including members of the ESKAPE group (Enterococcus faecium, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* spp.), frequently involved in hospital-acquired infections [5].

Bacteria can develop resistance to antimicrobial treatments through several mechanisms. At the molecular level, bacterial cells employ several strategies to evade antimicrobial activity [6]. A prevalent mechanism involves reducing the intracellular concentration of antimicrobial agents by increasing the expression of the efflux pump [7]. In addition, bacteria can modify their molecular targets, preventing antimicrobial binding and neutralizing therapeutic efficacy. Another strategy involves enzymatic degradation or modification of antimicrobial agents, making them ineffective before they can reach their targets [8]. Bacteria can also form biofilms, a protective microenvironment in which they can persist despite antimicrobial exposure [9]. However, despite recent initiatives including global surveillance programs and stricter antimicrobial regulation, the development of new antimicrobial treatments has not kept pace with the evolution of resistance. Most newly approved antibiotics belong to existing classes, offering only incremental improvements rather than fundamentally new mechanisms of action [10]. Therefore, there is an urgent need to refocus on alternative therapeutic strategies to contain the spread of AMR. This includes investment in rapid diagnostics, better infection control practices, and novel research approaches to understand resistance evolution and transmission.

2.2 Antimicrobial Peptides

In contrast to some traditional treatments, AMPs have emerged as promising candidates to face the AMR crisis, due to their broad-spectrum activity and mechanisms of action, bypassing conventional resistance strategies [11] [12]. These peptides are synthesized from prokaryotic entities to mammals and play a vital role as integral components of their innate immune defense mechanisms [13]. Several studies have shown that certain cationic AMPs, in addition to their antimicrobial action, can be toxic to cancer cells with no adverse effect on normal cells [14] [15] [16], making them candidates as new tumor treatment options. Some AMPs properties, such as amphipathicity, moderate hydrophobicity, and positive charge, cause therapeutic activity in cancers [17]. These AMPs, that also induce toxicity

in cancer cells, are called anticancer peptides. They were classified by Boohaker et al. [18] into three classes based on their mechanisms of action: 1) pore-forming peptides, 2) cell-penetrating peptides, and 3) tumor-targeting peptides.

Pore-forming peptides, such as Magainin II, are commonly a part of the primary immune defense system [19]. They induce necrosis or apoptosis in cancer cells. If negatively charged peptides attack cancer cells, they eventually lead to cellular lysis, then necrosis. Other ones disrupt the mitochondrial membrane and act through the induction of apoptosis [20]. The tumor targeting ones detect the integrin receptors on the cancer cell membrane in breast and lung cancer cells, brain tumors, and ovarian carcinoma cells [20]. Finally, cell penetrating peptides, such as BR2, developed by Lim et al. [21], have toxic effects in several in vitro cancer lines. These peptides have been used because they are involved in the delivery of anticancer drugs to cells [22].

In this way, AMPs represent a class of molecules with considerable therapeutic potential due to their dual ability to target both infectious agents and cancer cells. Their membrane disruption mechanisms, structural versatility, and selective cytotoxicity make them possible alternatives to conventional antibiotics and chemotherapeutics. As resistance to standard treatments continues to increase, AMPs offer a promising path forward in the search for multifunctional agents. This study builds on that potential by using computational tools to identify and predict AMPs with anticancer activity, with the aim of supporting the rational design of next-generation therapeutics.

2.3 Literature Review

A systematic literature review was conducted following PRISMA guidelines [23] using keywords such as *antimicrobial*, *anticancer* and *AMP* to locate relevant studies published in the last few years. Of 29 identified records, 20 records were screened after applying automated and manual exclusion criteria. One could not be recovered due to access restrictions, which resulted in 19 studies being included in the final review. Figure 1 illustrates the study selection process.

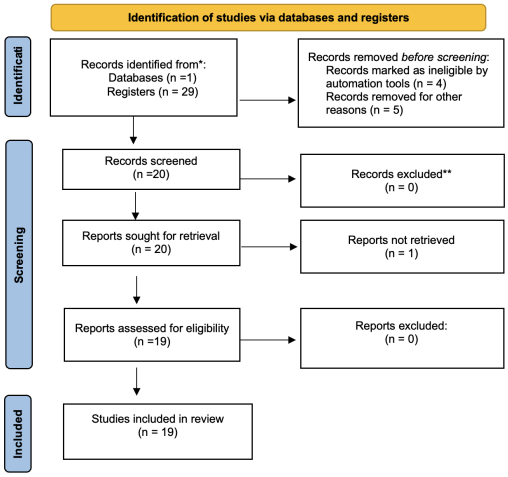

Fig. 1. PRISMA flow diagram (adapted) illustrating the process of selecting studies for systematic review.

Table 1 lists the antimicrobial peptides with experimentally validated anticancer properties identified in the review. The peptides originate from various sources (marine organisms, amphibians, insects, mammals, and synthetic origins), with the alfa helix being the predominant structure because of its amphipathic nature. The table includes peptide sequences, structural classifications, cancer types tested, and mechanisms of action.

Table 1. List of the 18 anticancer peptides (AMPs with anticancer activity), experimentally validated in the last few years, identified through a systematic literature review. The table includes peptide sequences, structural classifications, cancer types and described mechanisms of action.

Peptide	Source	Sequence	Structure	Type of Cancer	Mechanism of Action
LTX-315 [24]	Synthetic	KKWWKWIRW	α-helix	Melanoma, Sarcoma	Induces tumor cell death and acts as an in situ vaccine
Lactoferricin [25]	Milk	FKCRRWQWRMKKLGAPSITCVRRAF	β-sheet	Breast carcinoma, Leukemia	Induction of apoptosis via membrane interaction
Tachyplesin I, II, III [26]	*Tachypleus tridentatus*	KWCFRVCYRGICYRRCR	β-hairpin	Melanoma, Cervical cancer	Membrane disruption
Cecropin B [14]	*Hyalophora cecropia*	WKVFKKIEKMGRNIRNGIVKAGPAIAVLGEAKALSYGLRPG	α-helix	Ovarian, Endometrial cancers	Inhibition of cell viability
Cathelicidin-BF [27]	*Bungarus fasciatus*	KFFRKLKKSVKKRAKEFFKKPRVIGVSIPF	α-helix	Cervical, Liver, Breast cancer	Membrane disruption, cationic targeting
TP4 [28]	*Oreochromis niloticus*	FIHHIIGGLFSAGKAIHRLIRRRRR	α-helix	Sarcoma	Calcium overload, ROS production, mitochondrial hyperpolarization
Magainin II [29]	*Xenopus laevis*	GIGKFLHSAKKFGKAFVGEIMNS	α-helix	Bladder cancer	Pore formation in membranes
Pleurodicin [30]	*Pleuronectes americanus*	GWGSFFKKAAHVGKHVGKAALTHYL	α-helix	Hepatocellular carcinoma, NSCLC	Targeting microbial membranes
Epinecidin-1 [31]	*Epinephelus coioides*	GFIFHIIKGLFHAGKMIHGLVTRRRH	α-helix	Fibrosarcoma	Membrane attack and immune regulation
Periplanetasin-5 [32]	*Periplaneta americana*	GNNRGRVRVGRVGRVAGVGRGG	α-helix	Leukemia	Induces apoptotic and necrotic death
D-LAK-120A [33]	Synthetic	d-KLKLKLALKALKAALKLA	α-helix	Glioblastoma, NSCLC, Melanoma	Pore formation and ROS increase
Scyreprocin [34]	*Scylla paramamosain*	LPSVGLKALKTGNTGVRVQVCVVTAA	α-helix	Lung cancer	Membrane disruption and apoptosis induction
BR2 [35]	Derived from Buforin IIb	RAGLQFPVG $[RLLR]_3$	α-helix	Colon, Cervical carcinoma	Apoptosis induction
Figainin 1 [36]	*Boana raniceps*	FIGTLIPLALGALTKLFK	α-helix	Breast, Colorectal, Lung cancer	Membrane disruption, apoptosis
palustrin-Ca [37]	*Lithobates catesbeianus*	GFLDIIKDTGKEFAVKILNNLKCKLAGGCPP	Turn/α-helix	Cervical cancer	Membrane disruption
A4K14-Citropin 1.1 [38]	*Phyllomedusa bicolor*	GLWSKIKEVGKEAAKAAAKAAGKAALGAVSEAV	α-helix	Prostate adenocarcinoma, Glioblastoma	Membrane disruption
GA-K4 [39]	Synthetic	FLKWLFKWAKK	α-helix	Not specified	Membrane disruption
Pardaxin [46] [41]	*Pardachirus marmoratus*	H-GFFALIPKIISSPLFKTLLSAVGSALSSSGGQE-OH	Turn/α-helix	Prostate cancer, Glioblastoma	ROS production, membrane depolarization

3 Methodology

i) Dataset construction

To develop robust predictive models to identify antimicrobial peptides with anticancer activity, two curated datasets will be assembled: a positive class and a negative class. The positive dataset comprises AMPs feautures, selected according to predefined inclusion criteria under the PRISMA framework, with experimentally validated dual activity (antimicrobial and anticancer) extracted from public repositories, namely DRAMP [42] and CancerPPD [43]. The negative dataset consists of AMPs with confirmed antimicrobial activity but no documented anticancer effect. Only sequences lacking cytotoxic or anticancer annotations will be retained to serve as appropriate negative controls.

Following data collection, a comprehensive preprocessing pipeline will be implemented. This includes duplicate removal, sequence integrity checks, and the exclusion of entries containing non-standard amino acids. Feature scaling will be applied using either min-max normalization or z-score standardization. Features such as physicochemical descriptors and structural properties will be extracted from the amino acid sequences.

Subsequently, embedding generation will be performed to enhance the representational capacity of the input data. This will involve the use of high-order network embeddings or sequence-informed embeddings to encode latent structural and functional patterns within peptide sequences. Such techniques, as proposed by Liu et al. [44], aim to capture topological relationships and contextual similarities that are not easily discernible through hand-crafted features alone. These embeddings, combined with the extracted feautures, are expected to improve downstream model performance by offering richer and more abstract representations of peptide properties.

ii) Machine Learning and Deep Learning

With the processed feature matrices, a variety of ML and DL models will be explored. Traditional ML algorithms, including Random Forest (RF) and Support Vector Machine (SVM), will be considered for implementation as baseline classifiers to evaluate predictive performance. Simultaneously, deep learning architectures, specifically Convolutional Neural Networks (CNNs) and Recurrent Neural Networks (RNNs), will be developed to model sequential and spatial patterns in peptide sequences.

The overarching goal of the modeling process is to derive a set of rules or functions capable of mapping input (peptide sequence data) to output predictions that reflect phenotypic traits. Machine learning has proven to be particularly effective in resistance prediction tasks involving pathogens such as *Mycobacterium tuberculosis*, where resistance mechanisms are well characterized [45].

These advances extend to the classification of peptides. For example, xDeep-AcPEP employs convolutional networks and multitask learning to predict the efficacy of peptides in multiple types of cancer with high precision [46]. The iAMPCN model applies deep learning to classify various antimicrobial activities, including antibacterial and antiviral responses [47]. Hybrid frameworks such as ACPScanner [48] combine ensemble learning with AI-generated molecular descriptors not only to identify anticancer peptides but also to classify their functional subtypes [49]. Together, these innovations illustrate the growing capability of ML and DL frameworks to support high-throughput screening and rational design of multifunctional therapeutic peptides.

In this study, following the implementation of the prediction models, training will be performed using a stratified k-fold cross-validation to ensure a robust evaluation of model performance. Hyperparameter tuning will be performed via grid search and Bayesian optimization. Performance metrics including accuracy, precision, recall, F1 score, ROC-AUC, and the Matthews Correlation Coefficient (MCC) will be used to evaluate the effectiveness of the models. The highest performing model will be selected for downstream predictions on AMP sequences.

This framework is based on and aligns with previous research demonstrating the efficacy of computational approaches in peptide bioactivity prediction. Tyagi et al. [50] first proposed the use of machine learning models for the identification of ACPs, developing the AntiCP model using SVMs and hand-made descriptors. Recently, transformer-based models such as ProtBERT have shown significant improvements in representing biological sequences through contextual embeddings [51]. Integrating these developments into the present pipeline, involving advanced embeddings, is expected to substantially improve the identification of AMPs with dual antimicrobial and anticancer functions.

As described in this methodology, Figure 2 illustrates the overall workflow of our pipeline for AMP classification and prediction, showing each step from initial dataset construction and preprocessing to model training, evaluation and final prediction.

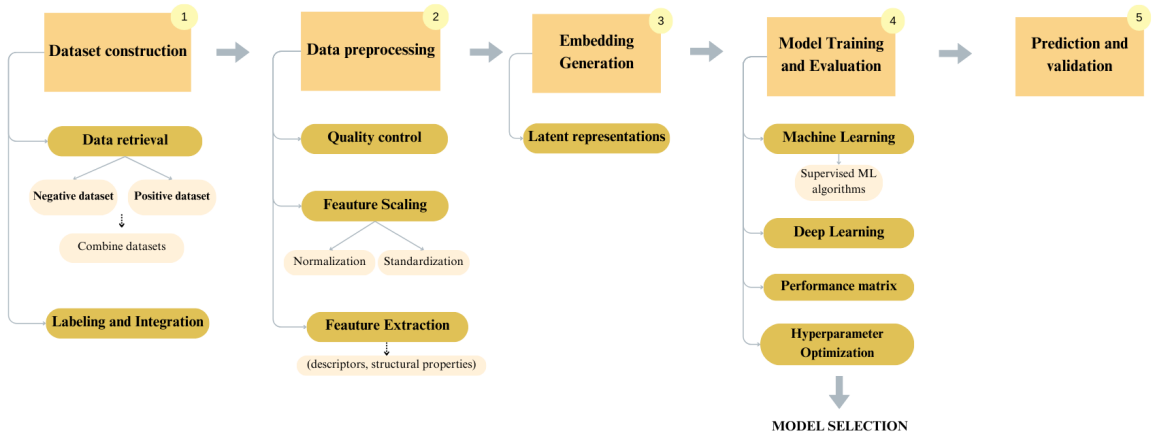

Fig. 2. Overview of the proposed pipeline for AMP classification and prediction, comprinsing five steps. comprising the following five steps:(1)Dataset Construction, integration of two curated datasets—one positive and one negative.(2)Preprocessing, removal of duplicates, sequence integrity checks followed by feature extraction (physicochemical descriptors and structural properties) and normalization.(3)Embedding Generation, application of high-order network or sequence-informed embedding techniques to capture latent structural and functional patterns within the peptide sequences(4) Model Training and Evaluation:Deployment of both traditional ML models and DL architectures to map sequence data to functional predictions, with model performance assessed through stratified k-fold cross-validation and optimization. Metrics are used for performance evaluation.(5) Prediction and Validation, implementation of the best-performing model for downstream predictions on new AMP sequences.

4 Expected Outcomes

This study aims to develop a robust and generalizable computational framework capable of accurately predicting antimicrobial peptides with dual antimicrobial and anticancer activity. By combining curated, high-quality datasets with advanced feature extraction techniques and embedding-based representations, the proposed models aim to support the high-throughput *in silico* screening of new candidate peptides. In doing so, the framework is designed to significantly reduce the time, cost, and experimental burden typically associated with therapeutic peptide discovery. Furthermore, analysis is expected to reveal sequence patterns and structural characteristics associated with dual functionality, providing valuable information for the rational design and optimization of multifunctional therapeutic agents. Ultimately, this work contributes to the collective effort to identify alternative strategies to combat antimicrobial resistance and cancer.

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