

REVIEW ARTICLE

Antimicrobial Peptides as Anticancer Peptides: The Strategies to Overcome Multidrug Resistance in Cancer

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Abstract. Cancer remains a leading cause of global mortality. Although chemotherapy is a primary treatment, its therapeutic efficacy is frequently compromised by multidrug resistance (MDR). Multiple factors contribute to this resistance, including ABC transporter-driven drug efflux, evasion of cell death, altered autophagy, tumor microenvironment changes, and persistent cancer stem cells. While MDR has been widely studied, we still lack a clear, comprehensive picture of how the structure of antimicrobial peptides (AMPs) helps them act as anticancer agents and break through this resistance. In this review, we cover the sources, structural traits, structure-activity links, and cancer-targeting abilities of AMPs. This review highlights major MDR mechanisms and explores how AMPs defeat treatment limits through varied actions, from membrane disruption and ROS production to immune modulation, mitochondrial damage, and ABC transporter blockade. Additionally, it also examines chemical modifications, sequence engineering, and nanocarrier delivery systems designed to enhance peptide stability, targeting, and therapeutic efficacy. Overall, AMPs show strong potential as multi-target anticancer agents that can reduce both drug resistance and side effects. Still, issues like rapid breakdown in the body, low bioavailability, high production costs, and delivery obstacles limit their clinical use. Combining promising sequence engineering with innovative delivery systems will be key to overcoming these barriers and unlocking their therapeutic value.

Keywords: Antimicrobial peptides, Anticancer peptides, Multidrug resistance, Cancer chemotherapeutics, Peptide therapeutics

1. Introduction

1.1 Cancer and multidrug resistance (MDR)

Cancer continues to be a top public health concern and a chief cause of death across the globe. GLOBOCAN 2022 data highlight the scale of this issue, recording about 20 million

new cases and nearly 10 million deaths worldwide in 2022 (Bray et al. 2024). Beyond abnormal cell division, cancer involves dynamic genetic and epigenetic alterations. This ongoing evolution drives intratumoral heterogeneity, enabling cells to evade immune destruction, metastasize, and develop multidrug resistance (MDR) (Brown et al. 2023). Despite modern therapies, positive treatment responses are frequently hindered by drug resistance, which continues to present a major challenge in clinical oncology (Wei et al. 2025). Drug resistance is not an accident. It happens because cancer cells naturally learn to avoid dying, which is a major hallmark of cancer (Hanahan and Weinberg 2011). Cancer cells often resist chemotherapy by boosting anti-apoptotic proteins like Bcl-2 or suppressing cell death signals. This intrinsic survival strategy directly fuels MDR and makes tumors more aggressive (García-Aranda, Pérez-Ruiz, and Redondo 2018; Maji et al. 2018).

Holohan and colleagues defined drug resistance as an "evolving paradigm" where intratumoral heterogeneity enables pre-existing resistant clones to survive drug pressure, adapt, and expand (Holohan et al. 2013). Supporting this, Vasan and team proved drug resistance is multi-factorial, driven by gene mutations, alternate pathways, Epithelial-Mesenchymal Transition (EMT), and microenvironment factors (Vasan, Baselga, and Hyman 2019). At the molecular level, MDR involves reduced drug uptake and increased drug efflux via ATP-binding cassette (ABC) transporters, particularly P-glycoprotein, which pumps chemotherapeutics out of cells. Additionally, resistance is driven

by target protein mutations, enhanced DNA repair, and epigenetic modifications that alter gene expression without changing the DNA sequence (Mansoori et al. 2017; Kinnel et al. 2023).

Current studies extend beyond identifying MDR mechanisms to developing therapeutic solutions. To overcome resistance, researchers are using combination therapies, efflux pump inhibitors, and nanoparticles to bypass drug expulsion, moving these strategies closer to clinical reality (Wang, Zhang, and Chen 2019). Recent studies expand beyond traditional mechanisms to cover cancer stem cells, exosome-mediated resistance, and immune evasion, alongside emerging treatments like targeted nanomedicines and epigenetic therapy (Li et al. 2025).

1.2 Limitations of conventional chemotherapy

While chemotherapy remains a cornerstone of oncological treatment, its therapeutic index is severely restricted by narrow selectivity, off-target toxicity, and treatment-induced resistance (Undevia, Gomez-Abuin, and Ratain 2005). Because conventional chemotherapeutic agents act indiscriminately on rapidly proliferating tissues, off-target destruction of normal bone marrow cells induces severe myelosuppression, neutropenia, and anemia, which markedly heighten patient infection risks and impair clinical outcomes (Crawford et al. 2024). Furthermore, cumulative agent-specific toxicities frequently occur; for instance, platinum- and taxane-based regimens routinely cause chronic peripheral neurotoxicity and sensory deficits (Was et al. 2022), while anthracycline treatment carries a substantial risk of dose-dependent cardiotoxicity and heart failure that restricts cumulative dosing (Qiu, Jiang, and Huang 2023). Beyond direct organ toxicities, sub-lethal chemotherapeutic stress can inadvertently trigger an epithelial-mesenchymal transition (EMT) program in surviving malignant cells, promoting phenotypic plasticity, anti-apoptotic signaling, and enhanced metastatic competence (Vasan, Baselga, and Hyman 2019; Tomecka et al. 2024). Together, these off-target toxicities and therapy-induced adaptations impose strict

dose limitations that compromise treatment continuity and foster disease recurrence (Garg et al. 2024).

1.3 Antimicrobial peptides (AMPs) as a promising therapeutic strategy

To circumvent the limitations and multi-tiered resistance mechanisms of conventional chemotherapeutics, research has focused increasingly on antimicrobial peptides (AMPs), also designated as host defense peptides (HDPs). Naturally occurring across virtually all living organisms as evolutionarily conserved components of innate immunity, AMPs are short, gene-encoded oligopeptides (typically 6–50 amino acids) defined by a net positive charge and an amphipathic spatial conformation. While historically characterized by their rapid, broad-spectrum bactericidal activity, many AMPs, termed anticancer peptides (ACPs), also exhibit potent and selective cytotoxicity against treatment-refractory and multidrug-resistant (MDR) human malignancies (Jafari et al. 2022; Bahar et al. 2025).

1.3.1 Structural Background: Why are cancer cells a target of AMPs?

MDR bacteria and cancer cells share a strong negative membrane charge driven by phosphatidylserine and mucins, enabling cationic AMPs to selectively target and disrupt both cell types. This structural similarity enables cationic AMPs (CAMPs) to act on both bacteria and cancer cells, driven by their characteristic amphipathic cationic structure. Mechanistically, malignant transformation disrupts normal membrane asymmetry via altered flippase and scramblase activity, leading to the pathological externalization of anionic phosphatidylserine (PS) to the outer leaflet. Combined with upregulated surface sialylation, O-linked mucins, and heparan sulfate proteoglycans, cancer cell surfaces develop a pronounced electronegative charge that closely mirrors the anionic lipid architecture of bacterial cell envelopes (Valenti et al. 2022; Gaspar, Veiga, and Castanho 2013). In contrast, healthy mammalian cell membranes maintain a neutral, zwitterionic outer leaflet

enriched in phosphatidylcholine and sphingomyelin, which protects them from non-specific electrostatic engagement (Lee et al. 2023)

1.3.2 Mechanism of action: Why AMPs beat MDR

Unlike conventional drugs that rely on specific enzyme targets, AMPs primarily act via membrane lysis by disrupting lipid bilayers through pore formation and making it difficult for cancer cells to develop resistance through target mutations (Xiaofang Luo et al. 2025). Additionally, certain AMPs like HX-12C inhibit ABCB1 (P-glycoprotein or MDR1) efflux pumps, restoring intracellular chemotherapeutic accumulation and reversing multidrug resistance alongside their own direct cytotoxicity (Luo et al. 2020). This discovery highlights the synergistic potential of AMPs alongside traditional chemotherapy, offering a targeted solution to the efflux pump resistance mechanisms described by (Mansoori et al. 2017). Thirdly, by targeting B-cell lymphoma/leukaemia-2 (BCL-2) proteins alongside membrane disruption and efflux inhibition, AMPs employ a multi-target strategy that drastically reduces resistance compared to single-target chemotherapy (Luo et al. 2025)

2. Antimicrobial Peptides: Biological Characteristics and Anticancer Properties

2.1 Definition, sources, and classification

Antimicrobial peptides (AMPs), or Host Defense Peptides (HDPs), are short-chain molecules typically composed of 6 to 50 amino acids. Conserved across nearly all kingdoms of life from prokaryotes to mammals, AMPs function as primary effectors of the innate immune system, serving as an initial defense against invading pathogens (Jafari et al. 2022; Bahar et al. 2025). Characterized by a net positive charge and amphipathic structure, AMPs rapidly disrupt pathogen membranes to kill bacteria, fungi, viruses, and parasites without inducing antibiotic-style resistance (Rima et al. 2021). AMPs serve a dual role as both direct antimicrobial agents and immunomodulators. In cancer treatment, this

ability to shape immune responses offers significant potential for use alongside conventional immunotherapies (Wu et al. 2022). Recent research reveals that AMPs possess potent anticancer activity alongside their antimicrobial properties. This dual capacity has driven strong interest in developing AMP-based cancer therapeutics. Anticancer peptides (ACPs) represent a specialized functional subgroup of AMPs that exhibit selective cytotoxicity against malignant cells (Zare-Zardini et al. 2024).

AMPs can be found from various sources as follows: Plant-derived AMPs, isolated across various plant organs, are characterized by high cysteine content and multiple disulfide bonds, which grant them exceptional thermal, chemical, and proteolytic stability (Tang et al. 2018). Plant-derived AMPs display substantial structural and functional diversity, encompassing major classes such as defensins, thionins, lipid transfer proteins, hevein-like peptides, snakins, and cyclotides (Tam et al. 2015; Tang et al. 2018). Within the defensin class, *Nicotiana glauca* defensins 1 (NaD1) from *Nicotiana glauca* targets fungal pathogens and selectively lyses cancer cells by binding surface phosphatidylinositol 4,5-bisphosphate (PIP₂) (Hayes et al. 2018; Baxter, Poon, and Hulett 2017), while NaD2 disrupts membrane integrity to induce apoptosis in vitro (van der Weerden, Nicole and Anderson 2013). Among cyclotides, kalata B1 from *Oldenlandia affinis* incorporates a unique cyclic cystine knot (CCK) motif stabilized by three disulfide bonds, rendering it exceptionally resistant to heat, pH variations, and enzymatic degradation which is a profile ideal for therapeutic scaffolding (Craik et al. 1999; Craik et al. 2006). Similarly, cycloviolacins from *Viola odorata* target surface phosphatidylethanolamine to permeabilize cancer cell membranes, prompting rapid intracellular leakage and cell death (Burman et al. 2011; Craik and Du 2017). Furthermore, thionin found in species such as *Triticum aestivum*, *Hordeum vulgare*, and various Brassicaceae, consist of 45–48 cysteine-rich amino acids that disrupt lipid bilayers, demonstrating clear potential to trigger cancer cell death through combined membrane

disruption and apoptotic pathways (Nawrot et al. 2014; Stec 2006). Animal-derived AMPs, such as those from amphibians (*Litoria*, *Rana*, *Bombina*, and *Phyllomedusa*), are rich sources of anticancer AMPs, most of which including magainins, discovered in the early 1980s which adopt an α -helical structure (Zhang 2025). Insects AMPs form a vital innate defense against diverse pathogens (Wu, Patočka, and Kuča 2018), beginning with the 1981 discovery of cecropin from *Hyalophora cecropia* (Buonocore et al. 2021). These peptides fall into three main structural classes: cysteine-free α -helical peptides, cysteine-rich β -sheet peptides with 3–4 stabilizing disulfide bonds, and proline- or glycine-rich peptides (Wu, Patočka, and Kuča 2018). Other notable families include ant venom ponerins and glycine-rich bacterial inhibitors like attacins and dipterocins (Buonocore et al. 2021). Beyond antimicrobial activity, many insect peptides display promising cytotoxicity against breast, lung, leukemia, lymphoma, and melanoma cancer lines (Jafari et al. 2022). Marine organisms, particularly invertebrates, produce structurally diverse AMPs with strong potential as antimicrobial and anticancer agents (Wu et al. 2021). Mollusks, especially mussels, are second only to arthropods as the most studied marine invertebrate source of AMPs (Guryanova et al. 2023). Continuous exposure to seawater microorganisms as filter feeders has led mussels to evolve a strong innate immune defense. Their AMPs are typically cysteine-rich cationic peptides whose disulfide bonds create stable structures resistant to protease degradation (Wu et al. 2021). Mussel AMPs are classified into four main groups according to sequence and disulfide connectivity: defensins, mytilins, myticins, and mytimycins (Wu et al. 2021). The defensin MGD-1 from *Mytilus galloprovincialis* contains an N-terminal α -helix and two antiparallel β -strands similar to arthropod defensins. Mytilins are highly abundant peptides occurring in at least five isoforms (A–D, G1) whose high cysteine content yields a compact structure (Guryanova et al. 2023). Myticins, present in hemocytes and plasma, exhibit both antimicrobial activity and tissue-repair functions, such as inducing hemocyte

migration (Rey-Campos et al. 2020). Teleost fish are another prominent source of marine AMPs, including piscidins and pleurocidins. Piscidins represent the first AMPs discovered in vertebrate mast cells, originally isolated from hybrid striped bass (Silphaduang and Noga 2001; Masso-Silva and Diamond 2014). The α -helical peptide piscidin-1 disrupts plasma membranes to induce apoptosis and necrosis in HT1080 fibrosarcoma cells and suppresses cell migration (Lin et al. 2012). Likewise, pleurocidin from winter flounder and its derivative NRC-03 inhibit cancer cell growth by disrupting mitochondrial integrity and inducing apoptosis (Hilchie et al. 2015). Horseshoe crab hemocytes generate tachyplesin and polyphemusin family AMPs during immune responses. Tachyplesin, isolated from *Tachyplesus tridentatus*, is a 17-residue, arginine- and cysteine-rich β -sheet peptide stabilized by two disulfide bonds that targets bacterial lipopolysaccharides (Nakamura et al. 1988). When conjugated to an integrin-targeting RGD motif, RGD-tachyplesin demonstrated potent *in vivo* antitumor efficacy by significantly inhibiting tumor growth in both chicken embryo chorioallantoic membrane assays and syngeneic murine prostate and melanoma xenograft models through dual activation of Fas-dependent and mitochondrial caspase cascades (caspase-8, -9, and -3) without non-specific toxicity (Chen et al. 2001). Ribosomally synthesized by Gram-positive and Gram-negative bacteria since the 1925 discovery of *E. coli* colicin, bacteriocins offer narrow-spectrum target specificity that holds strong potential against multidrug resistance (Mihaylova-Garnizova et al. 2024). Human AMPs are produced in various tissues, primarily as defensins and cathelicidins. Humans express a single cathelicidin, LL-37 (cleaved from hCAP18), which is produced by diverse immune, epithelial, and cutaneous cell types (Khurshid et al. 2017). Within human neutrophils, LL-37 adopts an α -helical structure and coexists alongside β -sheet defensins HNP-1 through HNP-4 (Turner et al. 1998). Human AMPs circulate in biological fluids such as plasma, saliva, sweat, and peritoneal fluid at site-specific concentrations. Specifically, LL-37 reaches 0.2–0.5 μ M in

plasma, 0.01–1.1 μM in sweat, and 4–6 μM in saliva (Miao et al. 2024). Within the skin, cathelicidins and LL-37 originate from keratinocytes, eccrine glands, mast cells, and neutrophils, which also co-express human neutrophil peptides (HNPs) and LL-37 (Poindexter 2005). These diverse cellular sources establish an immediate defense network across pathogen-exposed barrier tissues (Choi and Mookherjee 2012).

2.2 Structural characteristics related to anticancer activity

Electric Charge (Net Charge): This is driven by arginine and lysine residues, cationic AMPs (+2 to +9 net charge) selectively bind negatively charged cancer cell membranes via electrostatic attraction before inducing membrane disruption (Costa et al. 2019).

Amphipathicity: Amphipathicity determines whether AMPs kill cancer cells through membrane disruption or intracellular targeting. Peptides with high amphipathicity efficiently insert into lipid bilayers to cause membrane destruction. In contrast, less amphipathic, highly charged peptides favor intracellular targets like DNA or mitochondria. Adjusting amphipathicity allows researchers to rationally direct peptide mechanisms of action (Liu et al. 2016).

Hydrophobicity: Hydrophobicity exhibits a non-linear relationship with ACP potency. In CM4 peptide variants, moderate hydrophobic enhancement improves lipid bilayer penetration and anti-breast cancer activity (Li et al. 2018), whereas excessive hydrophobicity induces self-aggregation, compromising selectivity and bioactivity (Yang et al. 2020). This optimal range agrees with machine learning and analytical studies establishing hydrophobicity as a critical variable in natural ACP design (Zare-Zardini et al. 2024; Saini et al. 2024).

ACP mechanisms span direct membrane disruption (barrel-stave, toroidal pore, and carpet models) and non-lytic signaling, including apoptosis, anti-angiogenesis, immunomodulation,

and anti-metastatic pathways (Norouzi, Mirmohammadi, and Tehrani 2022). This multi-targeted mode of action prevents the rapid emergence of resistance observed with single-target chemotherapeutics, establishing a key foundation for rational ACP design (Lath et al. 2023). Elucidating these mechanistic principles offers a crucial framework for engineering next-generation AMPs as targeted cancer therapies.

2.3 Selectivity toward cancer cells

Unlike conventional chemotherapeutics, cationic AMPs selectively target cancer cells over normal cells through electrostatic interactions driven by fundamental membrane charge differences. Cancer cells display a net negative surface charge which is promoted by externalized phosphatidylserine, mucins, gangliosides, and heparan sulfate, whereas normal membranes maintain a zwitterionic balance (Gaspar, Veiga, and Castanho 2013), granting AMPs enhanced cytotoxicity against malignant cell lines (Hoskin and Ramamoorthy 2008). Cationic AMP selectivity is driven by tumor-specific biophysical traits, including elevated sialic acid, increased membrane fluidity, microenvironmental acidity, and abundant microvilli (Riedl, Zweytick, and Lohner 2011). This selectivity is demonstrated by natural and engineered peptides, Scyreprocin induces ROS- and ER stress-mediated apoptosis in lung cancer cells without fibroblast toxicity (Yang et al. 2022). Lycosin-I targets leukemia phosphatidylserine to drive apoptosis, G1 arrest, and ferroptosis via PI3K/AKT/mTOR suppression (Zhang et al. 2024) and KT2 concurrently disrupts membranes, apoptosis, and autophagy in colorectal cancer cells (Maraming et al. 2019). Because drug-resistant lines frequently display heightened negative surface charges, AMPs retain potency against MDR cancers (Felicio et al. 2017). Notably, HX-12C reverses ABCB1/P-glycoprotein efflux by stimulating its ATPase activity to restore intracellular drug accumulation (Luo et al. 2020b), an approach further enhanced by nanoparticle-based tumor delivery systems (Dong et al. 2024).

2.4 Limitations: Normal cell toxicity and therapeutic selectivity window

Although AMPs possess the property of selectively destroying cancer cells as mentioned above, AMPs are not completely safe for normal cells. The same membrane-disrupting mechanism that provides anticancer effects may also affect normal tissues, especially at high concentrations. The instability and hemolytic toxicity of peptides remain significant factors limiting their clinical application. Moreover, certain AMPs exhibit substantial toxicity to all tested normal cell lines, including red blood cells, indicating low specificity and a narrow therapeutic window (Bahar et al. 2025; Dong et al. 2024).

To assess the balance between anticancer activity and safety toward normal cells, the Selectivity Index (SI) is commonly used, which is calculated as $SI = IC_{50}(\text{normal cells}) \div IC_{50}(\text{cancer cells})$. An SI value greater than 1 indicates that the AMP is more toxic to cancer cells than to normal cells. However, major challenges for AMPs include high toxicity, instability, limited cellular uptake, and high synthesis costs, which hinder their clinical approval (Dong et al. 2024).

Strategies for addressing this narrow therapeutic window include modifying the structure of AMPs, such as adding positively charged amino acids and unnatural bulky amino acids to the termini, in order to reduce toxicity to normal cells while maintaining anticancer activity. This also involves employing nano-drug delivery systems, which help preserve the anticancer efficacy of AMPs while preventing enzymatic degradation and reducing hemolytic toxicity (Chu et al. 2015; Varela-Qutián, Mendez-Rivera, and Bernal-Estévez 2025).

3. Multidrug Resistance in Cancer

MDR limits chemotherapy effectiveness as cancer cells evade diverse drugs through complex genetic alterations, increased efflux, apoptosis resistance, autophagy, and tumor hypoxia (Emran et al. 2022).

3.1 Major mechanisms of MDR

Driven by integrated genetic, epigenetic, metabolic, and microenvironmental factors (Li et al. 2025), multidrug resistance limits treatment efficacy primarily through three clinical mechanisms: increased transporter-mediated drug efflux, apoptosis evasion, and enhanced DNA damage repair (Kapse-Mistry et al. 2014).

3.1.1 Drug Efflux Pumps

Overexpression of ATP-binding cassette (ABC) transporters is a major driver of MDR. These proteins consume ATP to efflux chemotherapeutics from cancer cells (Emran et al. 2022). Classified into seven subfamilies (ABCA–ABCG) across 48 human genes (Sun et al. 2026), the key members mediating oncology drug resistance are P-glycoprotein (P-gp/ABCB1), MRP1 (ABCC1), and BCRP (ABCG2) (Chen et al. 2024).

P-glycoprotein (P-gp/ABCB1) and BCRP (ABCG2) represent core ABC transporters that drive multidrug resistance by actively expelling structurally diverse chemotherapeutics (Goebel, Chmielewski, and Hrycyna 2021; Choi and Yu 2014). BCRP acts as a homodimeric half-transporter that effluxes drugs like irinotecan, SN-38, gefitinib, and methotrexate (Noguchi, Katayama, and Sugimoto 2014), impacting both tumor sensitivity and systemic ADME profiles across ovarian (Maliepaard et al. 1999), breast, gastric, and colorectal cancers (Schellens et al. 2000). Working alongside vault-associated lung resistance protein (LRP) which mediates exocytic drug clearance (Emran et al. 2022), these pumps collaborate with auxiliary mechanisms such as ceramide metabolic shifts, enzymatic detoxification, organellar sequestration, and glutathione conjugation to reinforce cancer cell chemoresistance (Kapse-Mistry et al. 2014).

3.1.2 Apoptosis Resistance

Evasion of apoptosis drives multidrug resistance by blocking chemotherapeutic action (Ye et al. 2025), impairing both intrinsic (via mitochondrial)

and extrinsic (via death receptor) pathways that converge on effector caspase execution (Wolf 2023). As widespread drivers of carcinogenesis, TP53 mutations promote resistance to chemotherapy, radiotherapy, and immunotherapies (e.g., checkpoint inhibitors, CAR-T) by disabling apoptotic pathways and remodeling the tumor microenvironment to support growth (Wang et al. 2024). Imbalances in anti-apoptotic Bcl-2 family members (Bcl-2, Bcl-xL, Mcl-1) protect cancer cells from BAX/BAK-mediated mitochondrial apoptosis and drive chemoresistance, a vulnerability exploited by BH3-mimetic drugs designed to reactivate intrinsic cell death (Ramesh and Medema 2020). The eight-member IAP oncoprotein family (notably survivin and XIAP) drives chemoresistance by inhibiting caspases and promoting survival signaling, with survivin mediating doxorubicin and sorafenib resistance, while XIAP impairs gemcitabine and carboplatin response (Ye et al. 2025). Hyperactivated PI3K/AKT signaling promotes multidrug resistance by suppressing apoptosis (via Bcl-2, XIAP, and Bax regulation) and cross-talking with ABC transporters, GSK-3 β , NF- κ B, and mTOR pathways (Liu et al. 2020).

3.1.3 DNA Repair and Other Resistance Mechanisms

Chemotherapeutics (alkylating agents, platinum complexes, and topoisomerase inhibitors) induce cytotoxic double-strand DNA breaks that cancer cells manage through multi-tiered repair systems (BER, NER, MMR, MGMT) and replication stress responses like translesion synthesis and fork reversal (Nesic et al. 2025). Enhanced DNA repair via ERCC1-dependent nucleotide excision repair (NER) and MGMT-mediated alkylation reversal directly drives resistance to platinum agents (cisplatin/carboplatin) and temozolomide, respectively. ERCC1 expression predicts response rates and overall survival in platinum-treated cervical cancer (Du et al. 2023), whereas MGMT promoter methylation status serves as a key prognostic biomarker to guide temozolomide therapy in glioblastoma (Castresana and Meléndez 2023). Alongside efflux, apoptotic evasion, and DNA repair, cancer multidrug resistance is protected through coordinated

epigenetic shifts, non-coding RNAs, metabolic adaptations, and microenvironmental remodeling (Li et al. 2025b).

3.2 Pharmacokinetic delivery barriers in the tumor microenvironment

In addition to systemic side effects, the efficacy of conventional chemotherapy is compromised by biophysical and pharmacokinetic delivery barriers within the tumor microenvironment (TME) that directly foster multidrug resistance (Oluwajembola et al. 2025; Paresishvili and Kakabadze 2023). Many standard chemotherapeutics possess unfavorable physicochemical properties, including low aqueous solubility, poor bioavailability, and rapid systemic clearance, which severely diminish drug accumulation at the target tumor site (Chidambaram, Manavalan, and Kathiresan 2011; Wang et al. 2023). At the tissue level, dense extracellular matrix deposition, abnormal and leaky tumor vasculature, and impaired lymphatic drainage generate abnormally high interstitial fluid pressure (IFP) (Tang et al. 2021). These microenvironmental impediments create steep convective and diffusion barriers that prevent uniform drug penetration into distal and hypoperfused tumor compartments (Souri et al. 2022). Consequently, cancer cells residing within deep tumor regions are consistently exposed to sub-lethal therapeutic concentrations, driving clonal selection, phenotypic resistance, and multidrug-resistant relapse (Paresishvili and Kakabadze 2023). This underscores the critical need for alternative membrane-active agents, such as antimicrobial peptides (AMPs), that can circumvent these microenvironmental transport limitations (Oluwajembola et al. 2025).

4. Mechanisms by Which AMPs Overcome MDR

While standard chemotherapeutics fail when cancer cells mutate specific intracellular targets, cationic AMPs bypass target-mediated resistance by electrostatically binding negatively charged tumor membranes, a fundamental physical trait less susceptible to mutational escape (Zare-Zardini et al. 2024). AMPs thus counter multidrug

resistance through a tri-fold mechanism: direct membrane disruption, target-independent cell death, and immune system stimulation (Dong et al. 2024).

4.1 Membrane disruption

Unlike conventional chemotherapy, cationic AMPs selectively disrupt cancer membranes through electrostatic attraction to net-negative tumor surfaces, driven by externalized phosphatidylserine, sialic acid, and glycosaminoglycans (Tornesello et al. 2020). Because normal cell membranes present a zwitterionic, cholesterol-rich, neutral surface (Zare-Zardini et al. 2024), AMPs show minimal interaction with healthy tissues, drastically reducing off-target toxicity (Tornesello et al. 2020). Mechanisms of AMP-mediated membrane disruption are traditionally

categorized into the barrel-stave model (peptides form purely protein-lined pores), the toroidal pore model (peptides induce lipid curvature to form mixed peptide-lipid pores), and the carpet model (surface-bound peptides disrupt membranes via detergent-like action above a threshold concentration) (Figure 1). In reality, these three models represent theoretical extremes. How a peptide behaves varies based on its concentration and the specific makeup of the membrane (Wimley 2010). Because conventional MDR pathways (ABC efflux, target mutations, DNA repair) target drugs acting inside the cell, AMPs bypass resistance by physically disrupting membranes from the outside before cells can adapt. Furthermore, ABC transporters cannot efficiently efflux large, highly charged peptides, allowing AMPs to avoid the primary efflux-mediated resistance mechanisms that limit conventional chemotherapy (Dong et al. 2024).

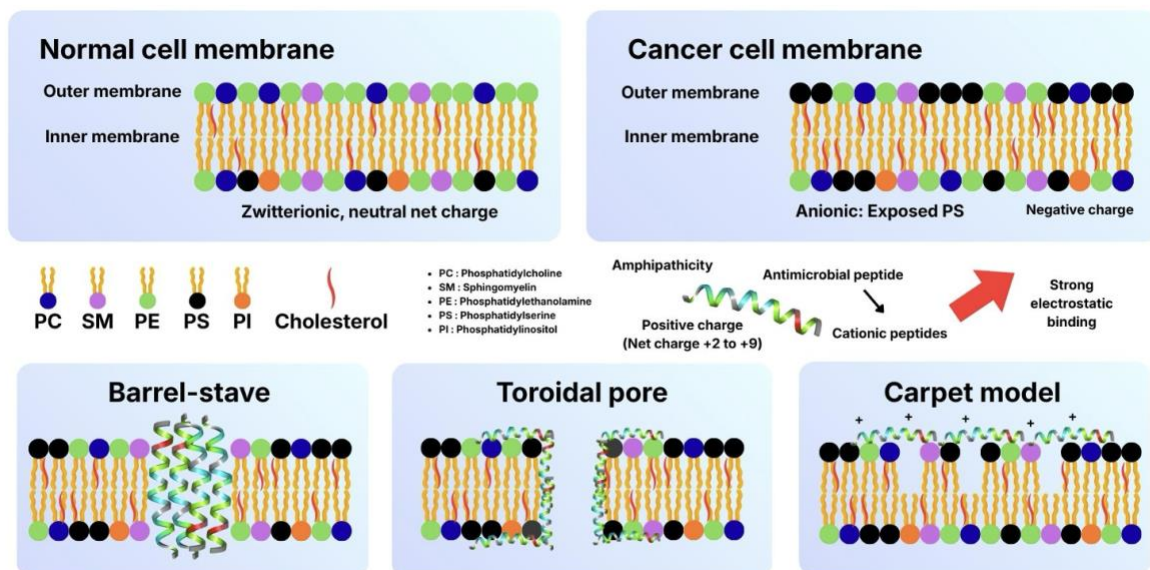


Figure 1: Mechanistic basis of AMP selectivity and membrane disruption

4.2 Induction of apoptosis and other cell death pathways

Beyond direct membrane lysis, many AMPs translocate into the cytoplasm without causing complete membrane destruction, triggering non-membranolytic apoptosis via intracellular pathways (Dong et al. 2024). For instance, pardaxin induces intrinsic apoptosis in HT-1080 fibrosarcoma cells by elevating ROS levels, collapsing mitochondrial membrane

potential, and activating caspases-3 and -7, a mechanism dependent on oxidative stress and caspase execution (Huang, Lee, and Chen 2011). This exemplifies how non-lytic AMPs trigger mitochondrial cell death by disrupting cellular redox balance and inducing cytochrome c release. Unlike conventional chemotherapeutics hindered by p53 mutations or Bcl-2 dysregulation, AMPs bypass established resistance nodes by driving direct ROS-mediated mitochondrial damage (Dong et al. 2024) and caspase-

independent cell death via calcium efflux (e.g., γ -thionin) (Flores-Alvarez et al. 2023). This mechanistic versatility prevents cancer cells from acquiring widespread cross-resistance across multiple death pathways.

4.3 Mitochondrial targeting and immunomodulation

Cationic AMPs can favorably accumulate in cancer cell mitochondria, driven by the highly negative mitochondrial membrane potential associated with Warburg-adapted cells (Zare-Zardini et al. 2024). This mitochondrial targeting can be further enhanced through structural modifications such as N-myristoylation (Li et al. 2018). At the mitochondria, these peptides promote ROS generation, cytochrome c release, and caspase activation through direct membrane permeabilization, thereby avoiding anti-apoptotic mechanisms associated with Bcl-2 and Bcl-xL overexpression (Wang et al. 2022; Lopez and Tait 2015). Beyond direct tumor lysis, AMPs like the human cathelicidin LL-37 serve as immunomodulators that bridge innate and adaptive anti-cancer immunity by regulating dendritic cells, macrophages, NK cells, and T lymphocytes (Mookherjee et al. 2020; Zare-Zardini et al. 2024). LL-37 drives dendritic cell maturation into cross-presenting CD103⁺/CD141⁺ subsets, enhancing CCR7-dependent lymph node trafficking and CD8⁺ T-cell priming to boost intratumoral immune infiltration and suppress tumor growth *in vivo* (Scott et al. 2002).

By enhancing host immunity, AMPs provide an essential orthogonal mechanism to clear chemoresistant clones, mitigating long-term recurrence risks. Significantly, AMPs remodel the tumor microenvironment by depleting immunosuppressive M2 macrophages and myeloid-derived suppressor cells while activating intratumoral CD8⁺ and CD4⁺ T cells, converting a tumor-permissive niche into an immunologically active antitumor environment (Zhang et al. 2022). Through the coordinated induction of membrane damage, mitochondrial apoptosis, and host immunomodulation into a single peptide, AMPs execute a multi-tiered attack (Figure 2) that makes simultaneous

resistance acquisition nearly impossible, offering a powerful platform against multidrug-resistant cancers (Dong et al. 2024).

5. Representative AMPs Against MDR Cancer

To illustrate the translational relevance of these mechanisms, this section examines natural and engineered AMPs evaluated in multidrug-resistant cancer models.

5.1 Natural antimicrobial peptides

Preclinical studies demonstrate that natural AMPs effectively circumvent multidrug resistance through distinct biophysical actions. For example, NK-2 (derived from human NK-lysin) kills P-glycoprotein-overexpressing lung (NCI-H460/R) and colorectal (DLD1-TxR) cancer cells while downregulating surface P-gp to restore adriamycin sensitivity (Banković et al. 2013). Similarly, Polybia-MPI (*Polybia paulista* wasp venom) retains full potency against K562/ADM leukemia cells, which exhibit over 200-fold doxorubicin resistance by folding into an α -helical structure that electrostatically permeabilizes tumor membranes regardless of efflux transporter status (Wang et al. 2009; Dong et al. 2024). Beyond non-specific membrane lysis, LL-37 fragments (LL17-32 and LL13-37) directly combat MDR by non-competitively binding ABCG2 (BCRP) and inducing its lysosomal degradation, effectively blocking drug efflux and restoring chemotherapy sensitivity in resistant cancer populations (Dong et al. 2024).

Melittin (bee venom) acts as a chemosensitizer in P-gp-overexpressing MCF-7/ADR breast cancer cells by inhibiting PI3K/Akt and NF- κ B signaling to downregulate P-gp and restore doxorubicin retention (Han et al. 2023). Complementing direct membrane disruptors like Buforin II and Magainin II, peptides such as pardaxin (T.C. Huang, Lee, and Chen 2011a), moricin (Ahmad et al. 2023), and Cecropin XJ (Trinidad-Calderón, Varela-Chinchilla, and García-Lara 2021) trigger apoptosis via mitochondrial, caspase, or Notch/NF- κ B pathways. While immunomodulators like LL-37 recruit adaptive T-cell responses to clear residual resistant clones (Findlay et al. 2019)

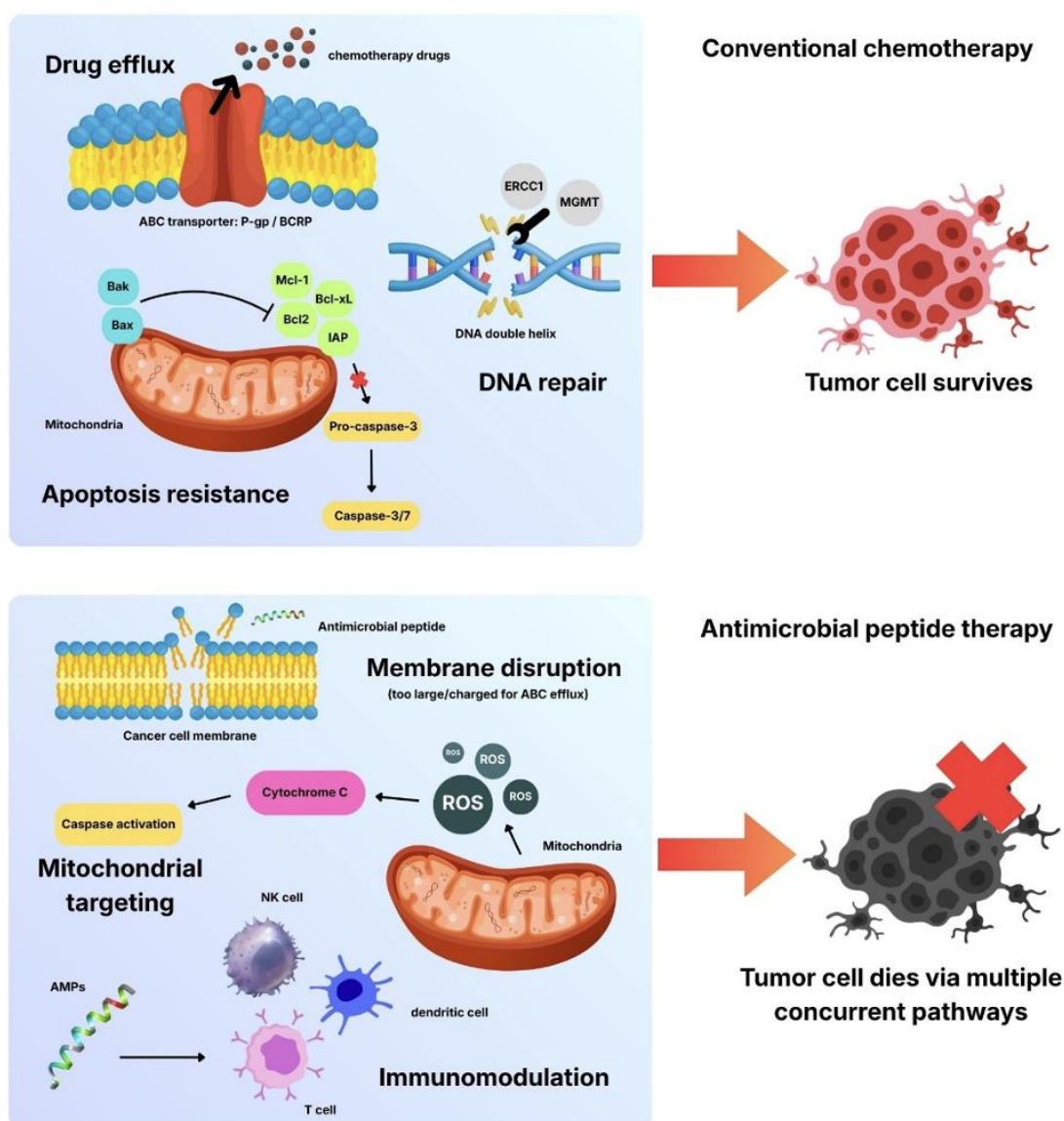


Figure 2: Multi-targeted actions of AMPs against cancer multidrug resistance

5.2 Synthetic or engineered antimicrobial peptides

Translational limitations of native AMPs, including short circulatory half-life, protease vulnerability, potential toxicity, and high synthesis costs, have driven chemical engineering strategies to optimize peptide stability and tumor selectivity (Trinidad-Calderón, Varela-Chinchilla, and García-Lara 2021). Substituting native L-amino acids with D-enantiomers overcomes systemic protease degradation (Hilchie et al. 2015). For instance, D-amino acid variants of the flounder-derived peptide NRC-03 exhibit increased metabolic stability and enhanced cytotoxicity against breast cancer cells relative to the native L-form,

offering a clear solution to the short half-life of natural AMPs. Incorporating non-natural amino acids like β -naphthylalanine alongside positively charged residues yield salt-resistant, low-toxicity peptides such as K4R2-Nal2-S1 (Chu et al., 2015). In preclinical animal models, systemic administration of the engineered peptide K4R2-Nal2-S1 markedly suppressed human lung tumor xenograft growth in nude mice while displaying exceptional salt tolerance, negligible erythrocyte hemolysis, and no detectable cytotoxicity toward normal human fibroblasts (Chu et al. 2015). In addition, integrating AMPs into nanocarriers, such as polymersomes co-encapsulating melittin and doxorubicin could overcome the systemic toxicity and hemolytic limitations of

free peptides while fully retaining P-glycoprotein downregulating activity via PI3K/Akt/NF- κ B pathway inhibition (Han et al. 2023).

Computational (*in silico*) design and machine learning algorithms now enable pre-synthesis optimization of peptide therapeutic indices by screening key physical and structural descriptors. Specifically, algorithms evaluate parameters including the mean hydrophobic moment (μ_H), helical wheel projection symmetry, charge distribution density, and spatial amphipathicity index to optimize electrostatic partitioning into anionic cancer bilayers while preventing the excessive hydrophobic clustering that drives erythrocyte hemolysis (Liscano, Oñate-Garzón, and Delgado 2020). By attacking multiple targets simultaneously, these dual-function peptides minimize resistance acquisition relative to single-target agents, leading to the clinical translation of several candidate peptides (Felicio et al. 2017).

Highlighting the structural and mechanistic diversity of natural and bioengineered AMPs evaluated in chemoresistant models, Table 1 compiles representative peptides tested against drug-resistant cancer cell lines, categorized by organ system to facilitate comparative assessment.

6. Challenges and Future Perspectives

Despite the mechanistic strengths of AMPs in overcoming MDR, their clinical translation remains constrained by systemic protease degradation, off-target cytotoxicity toward erythrocytes and healthy tissues, and suboptimal pharmacokinetic profiles (Ghaly, Tallima, and Shoeib 2026). This section details these primary translational barriers, surveys current bioengineering solutions, and highlights emerging research directions.

6.1 Stability and toxicity

Systemic instability and rapid renal clearance severely limit the clinical translation of AMPs. Serum proteases rapidly cleave peptide bonds in circulation, blunting *in vivo* activity despite high *in vitro* efficacy (Zhang et al. 2021). This short circulatory half-life requires high-

frequency administration or complex formulation strategies, creating significant barriers to patient compliance and therapeutic viability (Ghaly, Tallima, and Shoeib 2026). Although cationic AMPs exhibit preferential affinity for anionic cancer membranes over neutral zwitterionic normal cells, high peptide hydrophobicity can induce non-specific hydrophobic partitioning into neutral lipid bilayers, causing off-target cytotoxicity and red blood cell hemolysis. This narrows the therapeutic selectivity window. Therefore, rational optimization of the therapeutic index requires fine-tuning the balance between net positive charge and hydrophobic moment, ensuring selective disruption of cancer membranes without triggering bystander normal cell lysis (Vaezi et al. 2020; Pedron et al. 2023). Additionally, low natural extraction yields, and high synthetic production costs create substantial economic barriers to scaling AMPs for commercial clinical use (Dong et al. 2024). Protease resistance and tumor selectivity can be engineered through terminal protection, PEGylation (the process of adding polyethylene glycol (PEG) polymer chains to a drug, protein, or other molecule) (Li et al. 2021), cyclization, and D-amino acid substitution (e.g., D-NRC-03) (Hilchie et al. 2015). Furthermore, incorporating non-natural amino acids (e.g., K4R2-Nal2-S1) reduces off-target cytotoxicity (Chu et al. 2015). Precisely balancing net charge (Trinidad-Calderón, Varela-Chinchilla, and García-Lara 2021), hydrophobicity, and hydrophobic moment enables cationic peptides to retain stability and cancer specificity in physiological environments (Varela-Quitán, Mendez-Rivera, and Bernal-Estévez 2025).

6.2 Drug delivery strategies

Advanced delivery vehicles including hydrogels, self-assembled matrices, and nanoparticles might mitigate AMP instability and off-target toxicity. Specifically, PEGylated liposomal formulations (such as PEG-liposomal LL-37) reduce renal clearance and plasma protein binding, enhancing circulatory half-life, bioefficacy, and safety relative to free peptides (Zheng et al. 2025).

Nanoparticle encapsulation overcomes AMP toxicity in resistant cancers, as polymersomes co-loaded with melittin and doxorubicin prevent hemolysis while maintaining PI3K/Akt/NF- κ B-mediated P-gp suppression (Han et al. 2023). Crucially, PEGylated liposomes and polymeric nanocarriers provide steric shielding that suppresses plasma protein opsonization, masks foreign peptide epitopes from host neutralizing antibodies, and limits serum protease degradation, thereby markedly extending circulatory half-life and tumor bioavailability relative to unformulated native peptides. This approach highlights how nanocarriers optimize AMP pharmacokinetics by enhancing stability, enabling sustained release, and lowering systemic toxicity (Dong et al. 2024).

Microenvironment-responsive conjugates, such as pH Low Insertion Peptide (pHLIP) linked to the mitochondrial-disrupting peptide (KLAKLAK)₂ exploit Warburg-induced tumor acidity to achieve selective cell entry (Burns et al., 2016). Under acidic conditions, pHLIP undergoes a conformational transition that drives membrane insertion and targeted (KLAKLAK)₂-mediated cytotoxicity while remaining non-toxic to normal tissues at physiological pH, demonstrating a targeting strategy that extends beyond surface electrostatic attraction (Burns, McCleerey, and Thévenin 2016).

Conjugating AMPs with targeting moieties like LHRH-directed cecropin B ensures selective uptake in LHRH receptor-overexpressing ovarian and endometrial carcinomas (Li et al. 2016). Synergizing targeted delivery platforms with peptide design remains a key driver of clinical progress and regulatory approval for modern peptide drugs (Xiao et al. 2025).

6.3 Clinical translation and future research

Although there has been significant progress at the laboratory level, the number of AMPs that have undergone clinical testing in the context of drug-resistant cancer remains very limited.

In clinical translation, the first-in-class oncolytic cationic peptide LTX-315 demonstrated acceptable safety and verified immune-mediated antitumor efficacy in a dose-escalation Phase I clinical trial across patients with advanced solid tumors, triggering extensive tumor microenvironment remodeling, local necrosis, and systemic clonal CD8⁺ T-cell expansion (Spicer et al. 2021). Next-generation ACP development leverages bioinformatic screening and deep learning architectures to mine candidates from combinatorial peptide libraries and genomic databases (Varela-Quitán, Mendez-Rivera, and Bernal-Estévez 2025). By quantitatively modeling the hydrophobic moment (μ_H), net cationic charge distribution, and amphipathic face angles, computational frameworks can accurately predict anticancer selectivity and *in vivo* stability prior to solid-phase chemical synthesis, drastically reducing preclinical discovery costs and timelines (Liscano, Oñate-Garzón, and Delgado 2020), while AI and display libraries accelerate optimization against systemic degradation and clearance (Xiao et al. 2025).

Another noteworthy direction is the combining direct cytotoxicity with immune activation as seen with LL-37 (Findlay et al. 2019), and LTX-315 (Spicer et al. 2021), drives immunogenic cell death, enlisting host immunity to target residual, multidrug-resistant cancer cells (Zare-Zardini et al. 2024).

In summary, despite persistent challenges in peptide stability, toxicity, and systemic delivery, advances in structural optimization, nanomedicine, and clinical trials (e.g., LTX-315) highlight the strong therapeutic value of AMPs. Integrating computational design, tumor-microenvironment targeting, and immune system activation will be key to establishing bioengineered AMPs as viable treatments against drug-resistant tumors.

Table 1. Representative antimicrobial peptides (AMPs) reported to act against multidrug-resistant (MDR) cancer cells, including their biological source, the resistant cell line or model tested, and the principal mechanism by which each peptide overcomes drug resistance.

Peptide	Source	Cancer / Resistant Cell Line Tested	Key Mechanism to Overcome MDR	Reference
NK-2	Engineered from the active domain of human NK-lysin	NCI-H460/R (non-small cell lung cancer), DLD1-TxR (colorectal cancer) — both P-gp overexpressing	Direct cytotoxicity + downregulation of P-glycoprotein (P-gp) expression	(Banković et al. 2013)
Polybia-MP1	Venom of the Brazilian social wasp <i>Polybia paulista</i>	K562/ADM (leukemia; 201-fold doxorubicin resistant)	Direct Membrane Permeabilization: Pore formation driven by electrostatic interaction	(Wang et al. 2009)
LL17–32 / LL13–37	Fragments of human cathelicidin LL-37	ABCG2-overexpressing cancer cells	Transporter Inhibition & Degradation: Non-competitive ABCG2 inhibition + lysosomal degradation	(To et al. 2013)
Melittin (co-delivered with doxorubicin in polymersomes)	Bee venom (<i>Apis mellifera</i>)	MCF-7/ADR (breast cancer, doxorubicin resistant)	Transcriptional Downregulation: Inhibits PI3K/Akt and NF-κB signaling → downregulates P-gp	(Han et al. 2023)
L-K6	Lysine-rich cationic anticancer peptide	MCF-7/Adr (breast cancer, P-gp mediated doxorubicin resistance)	Direct Transporter Inactivation: Direct binding to P-gp → inhibits efflux function	(Wang et al. 2021)
Cecropin B–LHRH'	Cecropin B fused with an LHRH-targeting sequence	Drug-resistant ovarian and endometrial cancer cells	Receptor-Targeted Lysis: LHRH receptor-mediated binding + membrane lysis	(Li et al. 2016)
Lactoferricin B	Bovine milk (<i>Bos taurus</i>)	Cisplatin-resistant head and neck squamous cell carcinoma (HNSCC) cells	Immune/Checkpoint Modulation: Downregulation of PD-L1 → restores cisplatin sensitivity	(Zhang et al. 2018)
AMPs from housefly larvae	<i>Musca domestica</i> larvae	Bel-7402/ADM (hepatocellular carcinoma, multidrug resistant)	Transcriptional Downregulation: Downregulation of <i>MDR1</i> gene expression	(GUO, ZHAO, and CHENG 2019)
BMAP-28	Bovine cathelicidin (<i>Bos taurus</i>)	CEM-VLB (drug-resistant lymphocytic leukemia)	Direct Membrane Permeabilization: Target-	(Risso, Zanetti, and Gennaro 1998)

Peptide	Source	Cancer / Resistant Cell Line Tested	Key Mechanism to Overcome MDR	Reference
			independent electrostatic bilayer disruption	
Pardaxin	Secretion of the Red Sea Moses sole (flatfish)	HT-1080 (fibrosarcoma)	Mitochondrial/Apoptotic Pathway: ROS generation, mitochondrial collapse, caspase-3/7 activation	(Huang, Lee, and Chen 2011b)
Moricin	Silkworm (Bombyx mori)	MDA-MB-231 (triple-negative breast cancer)	Signal Transduction/Apoptosis: Notch/NF- κ B suppression + p53/Bax/caspase activation	(Ahmad et al. 2023)
D-NRC-03	D-amino acid analog of a winter flounder-derived pleurocidin	Human breast cancer cells	Protease Resistance/Lysis: D-amino acid substitution evades proteolytic cleavage	(Hilchie et al. 2015)

7. Conclusion

AMPs have evolved from innate defense peptides into potent anticancer agents targeting MDR. Their inherent cationic charge and structural diversity allow them to bypass traditional MDR mechanisms such as ABC efflux pumps, apoptotic resistance, and DNA repair pathways, which exploit the target-specific reliance and systemic toxicity of conventional chemotherapy. Consequently, AMPs offer a novel mechanistic approach to address the key limitations of current cancer treatments.

Unlike single-target chemotherapeutics, AMPs bypass multidrug resistance by acting through concurrent mechanisms: membrane disruption (barrel-stave, toroidal, carpet models), mitochondrial/ROS-mediated apoptosis, and immune activation. This multi-tiered action prevents rapid resistance acquisition, a concept validated experimentally by natural peptides (NK-2, polybia-MP1, melittin) that kill resistant cells or restore chemosensitivity, alongside engineered analogues optimized for safety and targeting.

However, translating AMPs to clinical oncology requires overcoming rapid serum degradation, hemolytic toxicity, and pharmacokinetic limitations. Ongoing solutions such as chemical optimization, nanocarriers, and computational design, are addressing these challenges, with clinical-stage candidates like LTX-315 demonstrating the feasibility of translating AMPs from bench to bedside.

In summary, AMPs offer a powerful strategy against multidrug-resistant cancers by leveraging non-traditional mechanisms that circumvent conventional resistance. Fusing peptide engineering, nanocarrier delivery, and cancer biology is critical to developing stable, non-toxic, and commercially viable AMPs, positioning them as key therapeutics in the future of oncology.

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