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Review Article

Antimicrobial Peptides as Next-Generation Anticancer Therapeutics: Mechanisms, Advanced Drug Delivery Systems, and the Frontier of Precision Oncology

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ABSTRACT

Antimicrobial peptides (AMPs) have emerged as a highly promising frontier in precision oncology, offering novel therapeutic mechanisms that distinctly differentiate them from conventional chemotherapeutic agents. This review comprehensively examines the major classifications of AMPs utilized in cancer research—including human, animal, marine, plant, and bacterial-derived sequences—alongside recent innovations in synthetic and structurally modified peptide engineering. The primary anticancer efficacy of AMPs stems from their cationic and amphipathic nature, which enables selective electrostatic targeting and mechanical disruption of negatively charged cancer cell membranes, effectively bypassing traditional multi-drug resistance pathways. Beyond direct membrane-lytic cytotoxicity, AMPs induce programmed cell death via mitochondrial depolarization, suppress tumor-supportive angiogenesis, and actively remodel the immunosuppressive tumor microenvironment to potentiate host adaptive immunity. Furthermore, we evaluate the expanding role of AMPs as advanced drug delivery vehicles, focusing on cell-penetrating peptides, peptide-drug conjugates, and self-assembling nanostructured hydrogels that optimize the delivery of traditional chemotherapeutic payloads across challenging biological barriers. Despite extraordinary preclinical success across diverse malignancies such as breast, lung, colorectal, and glioblastoma models, systemic clinical translation faces significant pharmacological hurdles, including low proteolytic stability in biological fluids, rapid renal clearance, off-target hemolysis, and high manufacturing costs. To bridge this translational gap, current research strategies are heavily leveraging rational sequence modifications, d-amino acid incorporation, chemical stapling, and smart stimuli-responsive nanocarriers. Ultimately, the integration of artificial intelligence and deep machine learning for de novo peptide design, paired with personalized neoantigen peptide profiling, promises to transform antimicrobial peptides from experimental laboratory candidates into highly selective, low-toxicity cornerstones of next-generation precision oncology.

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INTRODUCTION

1.1 The Evolution and Limitations of Contemporary Oncology

Cancer treatment has undergone a profound evolution, driven by the persistent global burden of malignant diseases as a leading cause of morbidity and mortality. Historically, the foundation of oncological care relied heavily on conventional modalities: surgery, chemotherapy, and radiotherapy. While these foundational approaches aim directly at tumor eradication and prolonging patient survival, their clinical utility is frequently bottlenecked by systemic toxicity, a lack of specificity for malignant tissues, and the inevitable emergence of cellular resistance [1, 2].

These off-target adverse effects—ranging from severe cardiotoxicity and neurotoxicity to debilitating hematological complications—not only impair the patient's quality of life but also restrict dosage intensity and treatment duration [7, 8]. In recent decades, a deeper understanding of molecular pathology has catalyzed the emergence of targeted therapies and immunotherapies (such as immune checkpoint inhibitors and chimeric antigen receptor T-cell therapies), transforming the prognostic outlook for aggressive or treatment-resistant malignancies [3, 4]. Precision oncology further refines this landscape by utilizing next-generation sequencing and biomarker profiling to tailor interventions to individual tumor characteristics [5].

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However, establishing uniform and durable treatment responses remains a formidable challenge. The complex architecture of the tumor microenvironment—characterized by severe hypoxia, aberrant vasculature, and a dense extracellular matrix—severely hampers drug penetration [9, 11]. Furthermore, intrinsic cellular heterogeneity and the survival of a resilient subpopulation of self-renewing cancer stem cells (CSCs) continuously fuel tumor recurrence, metabolic adaptation, and multi-drug resistance (MDR) phenotypes [9, 10]. Consequently, there is an urgent clinical imperative to develop innovative treatment paradigms that offer enhanced specificity and alternative therapeutic mechanisms. Emerging biophysical approaches—including nanotheranostics, microbial therapeutics, and advanced biomaterials—are currently being engineered to address these structural and biological barriers [2, 6, 12, 13].

1.2 Antimicrobial Peptides (AMPs) as Multifunctional Therapeutics

Antimicrobial peptides (AMPs), historically recognized as essential components of innate immunity across diverse biological phyla, represent a promising frontier in next-generation oncology. Characteristically short, these oligopeptides typically comprise between 6 to 100 amino acids and possess distinct cationic and amphipathic properties [14, 15]. Structurally, AMPs exhibit diverse conformational arrangements, including α-helices, β -hairpins stabilized by disulfide bridges, and extended or looped loops, all of which dictate their specific biological interactions [16, 17].

Beyond their primary role in clearing bacterial, fungal, viral, and parasitic pathogens, these molecules exert potent immunomodulatory and anti-inflammatory effects. This functional versatility has prompted a transition in nomenclature toward "host defense peptides" (HDPs), reflecting their broader systemic role in immune regulation and tissue homeostasis [18, 19]. Recently, AMPs have attracted significant attention for their unique anticancer properties.

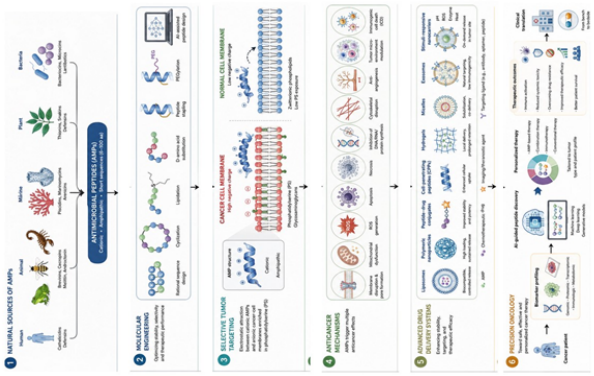
Unlike traditional chemotherapeutics that indiscriminately disrupt rapid cell division, certain AMPs demonstrate an inherent selectivity for malignant cells. This selectivity is predominantly driven by electrostatic interactions: the cationic peptides preferentially bind to the negatively charged phospholipids (such as phosphatidylserine) abnormally exposed on the outer leaflet of cancer cell membranes, leaving healthy, neutrally charged cells largely unaffected [22, 23]. Beyond initial membrane disruption, AMPs exert multifaceted anticancer effects. They can trigger intracellular cascades leading to apoptosis or necrosis, interfere with key signaling pathways governing tumor proliferation, inhibit angiogenesis, and modulate the local tumor microenvironment to stimulate systemic antitumor immunity [22, 24]. This multi-targeted mechanism radically differentiates AMPs from small-molecule drugs, making them inherently less prone to triggering the typical pathways of acquired multi-drug resistance.

1.3 Scope and Objectives of This Review

Despite their vast preclinical potential, the successful clinical translation of AMPs faces notable physiological hurdles. These include rapid proteolytic degradation in vivo, potential systemic cytotoxicity at elevated doses, and specific delivery challenges to dense tumor sites [22, 25]. To address these limitations, current bioengineering strategies focus on innovative chemical modifications—such as peptide lipidation, cyclization, and the design of self-assembled peptide nanostructures or chimeric fusion constructs [16, 20, 21]. The primary objective of this review is to comprehensively synthesize the contemporary knowledge surrounding the application of antimicrobial peptides as anticancer agents.

We elucidate the precise molecular mechanisms governing their selective cytotoxicity, investigate the structural properties and design criteria that dictate peptide efficacy, and highlight recent breakthroughs in advanced peptide delivery systems. Furthermore, we critically evaluate current preclinical and clinical evidence to outline translational challenges, discuss the synergistic potential of AMPs when combined with conventional therapies, and identify crucial knowledge gaps to guide future research directions in precision oncology [21, 22, 23, 24].

Figure 1 | Overview of antimicrobial peptides as next-generation anticancer therapeutics: from molecular design to precision oncology.



2. Overview of Antimicrobial Peptides

2.1 Definition, Structural Conformations, and Physicochemical Determinants

Antimicrobial peptides (AMPs), alternatively designated as host defense peptides (HDPs), constitute a structurally diverse and evolutionarily conserved class of small gene-encoded oligopeptides. Found ubiquitously across virtually all biological taxa—including plants, invertebrates, mammals, and microorganisms—these peptides serve as essential effectors of the primordial innate immune response [26, 27]. Typically ranging from 5 to 50 amino acid residues with molecular weights generally under 10 kDa, their relatively short primary sequences facilitate rapid, energetically efficient cellular synthesis and allow for high conformational plasticity [28]. Physicochemically, the functional versatility of AMPs is governed by two hallmarks: a net positive charge (typically ranging from +2 to +9 due to an abundance of lysine and arginine residues) and a highly amphipathic architecture [29]. This spatial segregation of hydrophobic and hydrophilic domains enables selective, electrostatically driven interactions with the negatively charged components of target membranes (such as lipopolysaccharides in Gram-negative bacteria or phosphatidylserine in malignant host cells) [16, 29]. Because non-cancerous mammalian membranes are predominantly composed of zwitterionic or neutral lipids, AMPs selectively bind to and disrupt pathogen or tumor membranes while leaving healthy host cells intact. Upon initial electrostatic docking, the hydrophobic regions of the peptide insert into the lipid bilayer, destabilizing membrane integrity through non-receptor-mediated pathways such as pore formation, membrane thinning, or total carpet-like dissolution [16]. Structurally, natural and engineered AMPs are broadly categorized into four primary three-dimensional conformations based on their structural geometry.

Linear molecules that adopt amphipathic helical structures only upon contact with hydrophobic membrane environments constitute the α-helical peptides, whereas rigid, cyclic, or open structures stabilized by intrinsic disulfide bridges form the β -sheet architectures. Additionally, extended structures represent peptides rich in specific amino acids like proline, glycine, or tryptophan that lack classical secondary folding, while looped topologies rely on single or multiple covalent bonds to form distinct loop constraints [16, 17]. Recent biophysical insights underscore that fine-tuning specific parameters—such as total helical content, net charge, overall hydrophobicity, and the hydrophobic moment—is critical for modulating the threshold between therapeutic potency and unwanted cytotoxic hemolysis [29]. Beyond canonical pathogen elimination, AMPs act as multi-functional signaling networks, functioning as immunomodulators, chemotactic factors, mitogens, and even antitumor agents, thereby seamlessly bridging innate and adaptive immune homeostasis [15, 26, 27]. Furthermore, certain sequences possess the intrinsic capacity to self-assemble into higher-order nanostructures, such as nanoparticles, nanofibers, or nanorods, which significantly boosts their biostability, local bioavailability, and target affinity [16].

2.2 Natural and Synthetic Sources: Biological Libraries and Engineering Paradigms

Natural Repositories of AMPs

Engineering Strategy	Mechanism of Action	Therapeutic Benefit

In nature, AMPs are synthesized either constitutively or via transcriptional induction to serve as immediate, frontline chemical barriers against bacterial, fungal, viral, and parasitic invasions. These endogenous molecules are sourced from diverse biological kingdoms, including microbial systems where bacteria produce an extensive array of bacteriocins to eliminate ecological competitors. For example, specific probiotic strains such as Lactobacillus fermentum secrete novel peptides capable of targeting opportunistic human pathogens, including Pseudomonas aeruginosa and Serratia marcescens [30]. Within the plant kingdom, defensins represent a prominent class of derived AMPs that contribute to systemic flora immunity by interacting specifically with fungal or bacterial membrane lipids, a mechanism frequently exploited in transgenic agricultural models to engineer robust, pesticide-free disease resistance in crops [31]. In higher vertebrates, host defense peptides are strategically localized within epithelial tissues, mucosal surfaces, and phagocytic granules. In humans, the primary families include α- and β -defensins as well as cathelicidins like LL-37, both of which demonstrate broad-spectrum microbicidal profiles alongside complex immunomodulatory, wound-healing, and tumor-homing capabilities [32, 33]. To organize this vast natural inventory, comprehensive digital platform tools—most notably the Antimicrobial Peptide Database (APD)—catalog thousands of distinct, verified sequences, categorizing them by origin, primary structure, and specialized bioactivities to serve as a foundational reference library [34].
Synthetic Optimization and Engineering Strategies

Despite their remarkable efficacy in vitro, native AMPs are frequently hindered by classic pharmacological limitations. These include high susceptibility to circulating proteolytic enzymes, rapid renal clearance, manufacturing scale-up bottlenecks, and toxicity toward normal eukaryotic membranes at elevated systemic concentrations. Consequently, advanced molecular engineering and chemical modifications are applied to tailor synthetic analogs with optimized pharmacokinetic profiles.

Table 1 | Engineering strategies for enhancing the therapeutic performance of antimicrobial peptides.

Rational Sequence Tuning	Strategic modulation of charge-to-hydrophobicity ratios [29, 35].	Enhances membrane selectivity; reduces hemolytic toxicity.
Fatty Acid Conjugation	Covalent attachment of hydrophobic lipid tails (lipidation) [36].	Increases membrane insertion kinetics and extends in vivo half-life.
Peptide Cyclization	Introducing disulfide bonds or hydrocarbon staples [16].	Restricts conformational flexibility, shielding the backbone from proteases.
Computational Modeling	Leveraging machine learning algorithms and deep learning architectures [16, 37].	Enables high-throughput de novo motif discovery, minimizing trial-and-error synthesis.

To produce these optimized agents at scale, researchers rely on a dual paradigm consisting of solid-phase chemical synthesis and recombinant DNA technologies. While chemical synthesis offers unmatched versatility in incorporating non-natural amino acids or precise chemical modifications, recombinant expression systems using microbial hosts such as Escherichia coli or yeast provide a highly cost-effective route for the mass production of longer, structurally complex therapeutic peptides [38]. Recent advances in peptide engineering have substantially expanded the therapeutic potential of antimicrobial peptides by improving their stability, selectivity, and pharmacological performance (Table 1).

Representative molecular engineering approaches used to improve the pharmacokinetic and pharmacodynamic properties of antimicrobial peptides, together with their mechanisms of action and therapeutic advantages for anticancer applications.

2.3 Structural Features of Antimicrobial Peptides

Secondary Structure and Amphipathicity

Antimicrobial peptides (AMPs) exhibit distinctive structural hallmarks that dictate their biological activities, most notably their capacity to selectively interact with and disrupt target cell membranes. These key structural determinants involve a delicate interplay of amphipathicity, secondary structure conformation, net charge distribution, and specific amino acid composition, which collectively modulate their antimicrobial potency, targeting selectivity, and systemic toxicity profiles. A defining characteristic of AMPs is their ability to adopt stable, amphipathic secondary structures—most commonly α-helices and β -sheets—which establish a distinct spatial segregation of hydrophobic and hydrophilic residues. This structural amphipathicity facilitates initial electrostatic attraction to negatively charged biological membranes and subsequent partitioning into the hydrophobic lipid bilayer, leading to catastrophic membrane disruption [39, 40]. For instance, α-helical AMPs are often unstructured in aqueous environments but adopt amphipathic helices upon membrane contact, orienting their hydrophobic residues toward the fatty acid core and their positively charged residues toward the hydrophilic lipid headgroups [41]. The degree of helical content strongly correlates with both cytotoxicity and specificity, meaning that peptides with optimized helicity maintain high lytic potency while minimizing unwanted hemolytic activity against healthy host cells [40]. Conversely, β -sheet AMPs are structurally stabilized by rigid intra-chain disulfide bonds, arranging alternating hydrophobic and hydrophilic side chains to execute membrane targeting [42]. Interestingly, certain AMPs retain robust membrane-binding capabilities without adopting classical α-helix or β -sheet motifs; for example, specific diastereomeric peptides preserve the spatial segregation of polar and nonpolar surfaces despite a total loss of regular secondary folding [41].

Charge and Hydrophobicity

The baseline targeting selectivity of AMPs is largely driven by their cationic nature, with net positive charges typically ranging from +2 to +9. This high positive charge density enables preferential binding to anionic microbial or malignant membranes over the zwitterionic, neutral outer leaflets of healthy mammalian host cells, though the spatial distribution and specific identity of these cationic residues profoundly affect overall potency [39]. Arginine and lysine are the predominant positively charged amino acids found within these sequences. However, subtle biophysical differences between the guanidinium group of arginine and the amine group of lysine significantly alter the kinetics of membrane translocation and lipid headgroup deformation [43]. Complementing this electrostatic drive, hydrophobic amino acid residues—particularly tryptophan, phenylalanine, leucine, and isoleucine—facilitate direct insertion into the lipid bilayer by anchoring the peptide backbone within the hydrophobic core [44]. Striking a precise balance between hydrophobicity and net charge is a critical design bottleneck in peptide engineering, as excessive hydrophobicity triggers non-specific hydrophobic associations with normal host cell membranes, escalating systemic toxicity, whereas insufficient hydrophobicity renders the peptide incapable of effective membrane permeabilization [45, 46].

Conformational Constraints and Stability

Beyond naturally occurring secondary structures, structural modifications such as backbone cyclization and the incorporation of non-proteinogenic amino acids are widely used to enhance conformational rigidity, which directly correlates with heightened therapeutic activity and proteolytic stability. For example, head-to-tail cyclization of short oligopeptides can drastically improve membrane-binding affinity, antimicrobial potency, and cell selectivity by locking the peptide into an optimal amphipathic conformation [43]. Similarly, the strategic substitution of native residues with α,α-disubstituted amino acids or the implementation of covalent cross-linking architectures, commonly known as side-chain stapling, preserves the required amphipathic topographies while shielding the peptide backbone from circulating proteolytic degradation [39]. This

optimization is further supported by specific amino acid distribution patterns, where the relative positioning of hydrophilic and hydrophobic segments along the primary sequence controls the overall hydrophobic moment; systematic studies confirm that alternating arrangements of charged and non-polar residues optimize membrane-disruptive efficacy and targeted selectivity [42].

2.4 Structural and Functional Divergence: AMPs versus ACPs

While antimicrobial peptides (AMPs) and anticancer peptides (ACPs) share broad architectural features—such as short sequence lengths, cationic charges, and amphipathic structures—they differ fundamentally across their target specificities, exact modes of action, and clinical applications(Table 2).

Table 2 | Structural and functional distinctions between antimicrobial peptides and anticancer peptides.

Comparative Parameter	Antimicrobial Peptides (AMPs)	Anticancer Peptides (ACPs)
Structural Motifs	Short, cationic, and amphipathic sequences optimized for microbial lipid envelopes [22, 24].	Engineered with specialized tumor-homing motifs and modifications to lower eukaryotic clearance [22, 24].
Primary Mechanism	Membrane lysis via pore formation, carpet models, or intracellular target inhibition [47].	Electrostatic targeting of phosphatidylserine, triggering apoptosis, necrosis, or mitochondrial lysis [48, 49].
Target Specificity	Broadly selective for prokaryotic, fungal, and viral membranes based on surface charge density [22, 24].	Selective for malignant host cells by exploiting altered tumor physiology and surface glycosylation [22, 24].
Biological Role	First-line innate immune defense, pathogen clearance, and localized inflammation control [24, 48].	Direct tumor cytotoxicity, microenvironment modulation, and induction of systemic antitumor immunity [24, 48].
Clinical Target	Developed primarily as alternative therapeutics for multi-drug resistant infectious diseases [48, 50].	Developed as precision oncology agents, often serving as adjuvants to reverse chemotherapy resistance [48, 50].

Comparison of antimicrobial peptides and anticancer peptides according to structural characteristics, biological targets, mechanisms of action, and therapeutic applications.

2.5 Structural and Functional Classification Systems

Classification Based on Structure

The immense structural diversity of host defense molecules necessitates a systematic classification framework based on their three-dimensional geometric conformations. The first primary group comprises the α-helical peptides, exemplified by magainins and cecropins, which remain predominantly unstructured in aqueous solutions but fold into amphipathic helices upon interaction with lipid bilayers to drive membrane permeabilization [51]. The second major group consists of β -hairpin or β -sheet peptides, such as defensins and tachyplesins, which are rigidified by internal disulfide bridges; their compact size and heightened protease resistance make them highly attractive scaffolds for multi-functional drug design [17]. A third category includes extended or loop peptides, which lack canonical α-helix or β -sheet folding and instead adopt highly flexible conformations rich in specific amino acids like tryptophan, proline, or arginine to execute membrane insertion [52]. Finally, cyclic peptides form a distinct structural class where covalent cyclization imposes strict conformational constraints, drastically increasing resistance against serum proteases while enhancing targeted lytic activity [17].

Classification Based on Function

Functionally, these molecules can be categorized by their specific clinical targets and biological activities, though significant crossover exists between groups. Antibacterial peptides represent the largest functional category, targeting bacterial pathogens by disrupting outer membrane integrity or translocating internally to halt nucleic acid and protein biosynthesis [53]. Antifungal peptides operate through overlapping mechanisms but specifically target fungal cell wall components and lipid rafts to induce cellular leakage [54]. Antiviral peptides represent a specialized subset capable of neutralizing both enveloped and non-enveloped viruses, achieving this by direct viral envelope disruption or by competitively blocking viral entry and intracellular replication pathways [55]. Antiparasitic peptides deploy non-specific membrane lytic mechanisms against protozoan parasites like Plasmodium and Leishmania, though achieving high therapeutic indices in this category remains a clinical challenge [56]. Moving beyond direct pathogen elimination, immunomodulatory peptides regulate host inflammatory cascades, promote tissue wound healing, and recruit adaptive immune cells without asserting direct microbicidal pressure [53, 54]. Lastly, anticancer peptides function as a specialized oncology cohort, selectively binding to abnormally exposed anionic lipids like phosphatidylserine on tumor membranes to trigger programmed cell death and remodel the immunosuppressive tumor microenvironment [28].

Integrated Perspective on Structure-Function Relationships

These structural and functional classification systems are deeply interconnected rather than mutually exclusive. For instance, an individual α-helical peptide can simultaneously exhibit antibacterial and antiviral profiles, while a rigid β -sheet peptide may demonstrate both potent anticancer cytotoxicity and systemic immunomodulatory effects. Ultimately, the underlying structural conformation dictates the exact biophysical mode of action, membrane interaction kinetics, and overall cell specificity, driving contemporary peptide development strategies. Elucidating these intricate structure-function relationships through advanced biophysical techniques—such as nuclear magnetic resonance (NMR) spectroscopy—has been vital for mapping these mechanical dynamics and guiding the rational design of synthetic peptide analogs with maximized therapeutic profiles and minimal off-target toxicities [51].

3. Biological Basis of Anticancer Activity

3.1 Differences Between Normal Cells and Cancer Cells

Understanding the fundamental distinctions between normal and neoplastic cells is crucial for elucidating the biological mechanisms underlying anticancer peptide targeting. These differences span cellular behavior, metabolic pathways, genetic stability, and complex interactions with the local microenvironment, all of which contribute to the unique physiological profile of malignant cells. Normal cells maintain strict tissue homeostasis through tightly regulated processes, including asymmetric cell divisions that balance self-renewal and lineage differentiation to preserve cellular equilibrium. In contrast, tumor cell subpopulations, such as cancer stem cells, exhibit altered division patterns characterized by enhanced symmetric division, which continuously expands the pool of undifferentiated, tumorigenic cells. For instance, aberrant template DNA cosegregation during mitosis reflects a profound loss of asymmetric division control, directly correlating with tumor cell fate and repopulation capacity [57]. A metabolic hallmark of cancer cells is the comprehensive reprogramming of cellular pathways to meet the bioenergetic demands of rapid proliferation. Oncogenic signaling pathways, most notably the mechanistic target of rapamycin complex 1 (mTORC1), drive enhanced glycolytic flux—commonly recognized as the Warburg effect—alongside increased pentose phosphate pathway activity and accelerated de novo lipogenesis. These metabolic adaptations confer structural growth advantages absent in normal differentiated tissues, which rely predominantly on highly efficient oxidative phosphorylation under aerobic conditions [58]. Furthermore, comparison reveals significant upregulation of nucleotide metabolism and oxidative pathways in malignant lines,

contrasted with a pronounced downregulation of pathways governing cell communication, cell-adhesion molecules, and extracellular matrix interactions, a shift that reflects the loss of normal tissue architecture [59]. These behavioral shifts are driven by profound genetic and epigenetic lesions. Studies on tumor models harboring adenomatous polyposis coli (APC) mutations demonstrate that cellular context heavily influences gene regulation patterns and cellular plasticity, with mutant cells frequently displaying pluripotent stem cell-like profiles but biased differentiation propensities. Reversing these mutant gene functions can successfully restore normal differentiation patterns and suppress neoplastic growth, showcasing the therapeutic potential of targeting genetic context [60]. Additionally, cancer progression involves a process of clonal phenotypic selection, yielding heterogeneous cell populations with variable migratory capacities and intrinsic resistance to programmed cell death [61]. This malignant progression is further assisted by the disruption of competitive cellular interactions; while normal epithelial cells modulate tissue homeostasis by secreting tumor-suppressive microRNAs like miR-143 to inhibit nearby aberrant growth, this competitive balance is lost during tumor initiation [62]. Concurrently, both normal and malignant stem cells can exploit shared pathways, such as the miR-199a-LCOR axis, to evade interferon-induced differentiation, grant a survival advantage to the tumor compartment, and utilize aberrant signaling networks like the Hedgehog pathway to prevent baseline differentiation [63, 64]. Finally, cancer cells frequently adapt to, and survive, structural mitochondrial dysfunction, establishing a retrograde mitochondria-to-nucleus signaling crosstalk that alters nuclear gene expression to drive resistance, a phenomenon less prominent in normal host cells [65].

3.2 Negatively Charged Cancer-Cell Membranes as Selective Targets

Malignant cells present distinct alterations in plasma membrane composition and net surface charge, offering an ideal biophysical basis for selective targeting by membrane-active agents. Unlike normal eukaryotic cells, which maintain a charge-neutral outer leaflet, cancer cell membranes exhibit a pronounced net negative charge. In normal physiology, anionic phospholipids such as phosphatidylserine (PS) and phosphatidylethanolamine (PE) are strictly confined to the inner leaflet of the lipid bilayer. In cancer cells, this membrane asymmetry is structurally disrupted, causing the aberrant translocation and exposure of PS and PE on the outer leaflet [66]. Biophysical evaluations using model membranes mimic this altered architecture, confirming that the high proportion of outer anionic lipids enables selective electrostatic interactions with cationic molecules while sparing non-cancerous host cells that are rich in neutral or zwitterionic lipids [67, 68]. Single-molecule force spectroscopy has confirmed that cationic peptides display strong binding probabilities toward cancer cell membranes, driven by this surface charge differential [67].

When peptides are engineered with optimized hydrophobicity and high net positive charge, they generate selective membrane perforation, demonstrating up to a 200-fold selectivity index for triple-negative breast cancer lines over non-cancerous controls [68]. This selective cytotoxicity is well illustrated by molecules like cyclic gomesin, which induces membrane disruption preferentially in melanoma and leukemia lines without damaging normal erythrocytes [69]. Ultimately, alpha-helical peptides exploit this negative surface charge to drive membrane permeabilization, causing rapid loss of transmembrane potential and triggering downstream apoptotic or necrotic pathways [70]. Molecular dynamics simulations reveal that these peptides adsorb onto the membrane surface or penetrate into the core depending on the localized concentration of anionic lipids [71]. Furthermore, hybrid designs like AFP-KLA integrate tumor-specific targeting motifs with lytic sequences, facilitating selective membrane fusion and internalization to induce rapid mitochondrial membrane depolarization [72]. This structural divergence in lipid profiles is supported by clinical phospholipid profiling in non-small cell lung carcinoma versus normal epithelial tissues, emphasizing that exposed targets like PE represent a highly reliable vulnerability for target validation [66, 73].

3.3 Role of Membrane Fluidity and Surface Molecules in Anticancer Activity

The biophysical efficiency of anticancer peptides is heavily regulated by membrane fluidity and the layout of localized surface molecules, both of which dictate peptide docking, insertion kinetics, and cellular uptake mechanisms. Cancer cell membranes typically display altered fluidity metrics driven by modified lipid ordering and lower cholesterol-to-phospholipid ratios. Studies utilizing the cationic helical peptide L10-MMBen demonstrate that upon selective adsorption to anionic lipid domains, peptides can induce extensive membrane remodeling rather than simple pore formation. Specifically, the peptide extracts lipids to assemble double-layered peptide-membrane composites, a phase transition that immobilizes lipid lateral diffusion and drastically reduces overall membrane fluidity [74]. This physical immobilization paralyzes vital membrane-bound receptor functions, presenting a cytotoxic mechanism distinct from classical pore-forming lysis. Beyond physical fluidity, the overexpression of surface molecules—including phosphatidylinositol networks and sialic acid-containing oligosaccharides—increases the localized negative charge density, generating a strong electrostatic pull for incoming peptides [67]. To exploit these surface features, modern designs utilize multi-functional hybrid systems; for example, the AFP-KLA peptide couples a tumor-selective alpha-fetoprotein motif with a pro-apoptotic lytic sequence, shifting the internalization mode from simple diffusion to direct membrane fusion [72]. Similarly, co-administration strategies using tumor-penetrating vectors like iRGD, which binds to overexpressed alpha-v-beta-3 integrins and neuropilin-1 receptors, accelerate target site accumulation and endosomal escape, enhancing downstream apoptosis [75]. Molecular dynamics simulations confirm that these distinct biophysical responses are determined by the peptide's specific hydrophobicity, size, and secondary structure configuration. Peptides with lower hydrophobic partitions tend to remain on the surface causing structural deformation, whereas highly hydrophobic, amphipathic sequences insert deeply into the core to drive carpet or toroidal pore-forming lysis without relying on classical receptor-mediated endocytosis [70, 71].

3.4 Selectivity of Antimicrobial Peptides Toward Cancer Cells

The intrinsic selectivity of antimicrobial peptides (AMPs) for malignant cells represents a critical cornerstone of their translation into oncology. This targeting efficiency relies on the structural configuration of the peptide balancing against the altered biophysical traits of the tumor cell. As established, the primary driver is the electrostatic attraction between cationic AMP sequences and exposed outer-leaflet phosphatidylserine [48, 67]. However, secondary cell-surface modifications, such as aberrant glycosylation patterns, also play a key role. For example, N-myristoylated CM4 exhibits a 2- to 3-fold higher affinity for breast cancer cells over healthy tissue by interacting specifically with highly expressed sialic acid-containing oligosaccharides, such as O-mucin and ganglioside clusters, allowing for selective internalization and mitochondrial targeting [76]. This selective threshold is not governed by charge alone, but rather by an integrated interplay of sequence length, total hydrophobicity, helicity, and self-assembly capacity [77]. Single-molecule force spectroscopy confirms that high anticancer potency correlates directly with initial membrane binding probability [67]. To optimize this window, peptide designers often use imperfect amphipathic designs—such as introducing helix-disrupting residues or adjusting the hydrophobic arc—which preserves tumor-lytic activity while eliminating toxicity toward normal mammalian cell configurations [78]. The functional downstream consequences of this selective docking include immediate membrane permeabilization, severe mitochondrial dysfunction, massive induction of reactive oxygen species (ROS), and the activation of caspase-dependent apoptotic pathways. This is demonstrated by the peptide TP4, which induces ROS-dependent mitochondrial collapse in MCF-7 breast cancer lines while leaving normal MCF-10 epithelial cells unharmed [79]. Similarly, the KT2 peptide targets colon cancer membranes to trigger cytochrome c release while concurrently blocking survival pathways like autophagy [80]. To build upon these natural traits, current strategies focus on chemical modifications like N-myristoylation, the integration of tumor-homing ligands, and sequence alterations designed to widen the therapeutic index by suppressing baseline hemolytic activity [76, 78, 81].

3.5 Factors Affecting Peptide Activity Against Tumor Cells

The performance, safety, and therapeutic index of antimicrobial peptides and their anticancer derivatives are determined by a group of well-defined physicochemical, structural, and mechanical factors. These core parameters can be systematically organized by their functional impact on the target cell: Regarding physicochemical properties, cationicity represents the primary driver of initial performance, where an increase in net positive charge facilitates stronger electrostatic docking onto exposed

outer-leaflet anionic lipids [82, 83]. This must be carefully balanced by hydrophobicity; while hydrophobic residues are mandatory to anchor the peptide and drive membrane insertion, excessive hydrophobicity leads to non-specific hydrophobic partitioning into neutral membranes, causing severe hemolytic toxicity toward normal host cells [76, 82, 83]. Working in tandem with these traits is amphipathicity, the precise spatial segregation of these polar and non-polar faces, which allows the peptide to fold into membrane-active configurations necessary to execute membrane permeabilization [82, 84]. Structurally, secondary conformation plays an equally vital role, as most potent sequences depend on adopting a stable alpha-helical structure upon lipid contact. The presence of structural stabilizers, such as internal disulfide bridges, is often mandatory to preserve this active conformation under physiological stress; reducing these bonds frequently results in a total loss of lytic activity [84].

Furthermore, optimizing overall peptide length and sequence composition prevents premature clearance, while post-translational chemical alterations—such as N-myristoylation—can be deployed to elevate membrane affinity, cell entry kinetics, and mitochondrial targeting without compromising baseline selectivity [76, 83]. The resulting mechanisms of action can be split into direct physical disruption and programmed intracellular targeting. Many peptides achieve rapid tumor clearance by permeabilizing the plasma membrane via non-receptor-mediated pathways, inducing total loss of cellular integrity and necrosis-like cell death [83]. Alternatively, certain sequences translocate across the bilayer to target internal organelles, driving caspase-dependent apoptosis via mitochondrial outer membrane depolarization, cytochrome c release, and sudden reactive oxygen species generation, a dual necrosis-apoptosis mechanism that reduces the risk of acquired resistance [76, 84, 85, 86]. Ultimately, the optimization of the overall therapeutic profile requires a delicate structural balance, ensuring high cationicity to maintain tumor affinity alongside moderate hydrophobicity to suppress off-target hemolytic interactions, ensuring prolonged stability against circulating proteases in vivo [50, 82]. The biological performance of antimicrobial peptides is governed by multiple interdependent physicochemical parameters that collectively determine therapeutic efficacy and safety (Table 3).

Table 3 | Physicochemical determinants governing the anticancer activity of antimicrobial peptides.

Biophysical Factor	Core Mechanism of Action	Primary Therapeutic Benefit	References
Positive Charge (Cationicity)	Drives initial electrostatic docking onto exposed outer-leaflet anionic lipids.	Enhances binding affinity and target cell recognition.	[82, 83]
Hydrophobicity	Forces insertion of the peptide backbone into the fatty acid core of the bilayer.	Controls membrane permeabilization; must be balanced to limit hemolysis.	[76, 82]
Amphipathicity	Imposes structural segregation of polar and non-polar faces during folding.	Mediates effective membrane disruption and pore-forming transitions.	[82, 84]
Structural Stability	Preserves active alpha-helical or disulfide-bridged secondary conformations.	Maintains lytic activity and provides resistance against proteolysis.	[84]
Chemical Modifications	Introduces artificial lipid tails (e.g., myristoylation) or structural cyclization.	Elevates cellular entry kinetics and improves downstream organelle targeting.	[76]
Apoptosis Induction	Forces mitochondrial outer membrane collapse and cytochrome c release.	Triggers clean, controlled tumor clearance via programmed cell death.	[84, 85, 86]
Selectivity Optimization	Harmonizes total sequence charge with precise hydrophobic arc sizing.	Maximizes tumor-specific lysis while widening the systemic safety window.	[82]

Key structural and biophysical parameters influencing membrane interaction, intracellular activity, therapeutic selectivity, and overall anticancer efficacy of antimicrobial peptides.

4. Mechanisms of Antimicrobial Peptides in Cancer Treatment

4.1 Membrane Disruption and Pore Formation by Antimicrobial Peptides (AMPs)

Antimicrobial peptides (AMPs) represent highly promising candidates in oncological therapeutics primarily due to their capacity to selectively target and physically disrupt cancer cell membranes. A foundational mechanism of action involves non-receptor-mediated membrane permeabilization, frequently executed through the formation of stable, membrane-spanning hydrophilic pores that compromise cellular integrity. Molecular dynamics simulations have provided high-resolution insights into the exact thermodynamics governing this process, detailing how model alpha-helical peptides like aurein 1.2, melittin, and magainin 2 diffuse, cluster, and stabilize transmembrane openings within lipid bilayers. The free energy barriers regulating pore nucleation and subsequent expansion confirm that pore formation is a peptide-driven thermodynamic event, strictly dependent on localized peptide clustering thresholds and specific lipid-peptide electrostatic associations, including localized salt bridges [87]. Linear cationic peptides disrupt these bilayers by continuously adsorbing onto the anionic outer leaflet of the cancer cell, introducing severe mechanical strain that forces a pore-forming transition determined by the balance of peptide charge and topological lipid constraints. Notably, this biophysical interaction is governed by a dynamic negative feedback loop that limits maximum pore size and controls membrane permeability, directly impacting the peptide's targeting selectivity and structural potency against malignant cell lines [88].

Experimental verification in specialized cancer models supports these computational insights. For instance, cationic peptides derived from natural repositories like snake venom, such as Crotalicidin and NA-CATH-ATRA-1-ATRA-1, demonstrate powerful cytotoxicity against human breast cancer lines by inducing rapid membrane permeabilization. Treatment with these venom-derived sequences triggers a sharp increase in intracellular propidium iodide uptake—a direct indicator of compromised plasma membrane integrity—without immediately altering mitochondrial membrane potential or affecting apoptotic markers like caspase-9 and poly (ADP-ribose) polymerase (PARP), confirming a primary, rapid membranolytic mode of cell death [89]. Similarly, atomic force microscopy has revealed that the cationic peptide KT2 causes extensive structural lesions and defects across the plasma membrane of colon cancer cells, accelerating cellular leakage alongside the downstream activation of cell death markers [80]. However, the mechanical interplay between AMPs and living cell membranes is more complex than simple model membrane pore-formation indicates. In a dynamic in vivo tumor environment, transient membrane disruptions accompanied by rapid cytoplasmic leakage frequently dominate over organized, static pore complexes, highlighting the highly heterogeneous nature of biological bilayers [90]. Furthermore, certain advanced sequences bypass classical pore-forming mechanics entirely, killing the cell by accelerating localized lipid transport and scrambling processes that destroy membrane asymmetry, triggering lethal downstream signaling cascades without ever punching a standard channel through the wall [91].

4.2 Mitochondrial Damage and Apoptosis Induction

Mitochondrial degradation and the subsequent activation of programmed

cell death pathways represent a major route through which AMPs exert their anticancer efficacy. These peptides consistently trigger apoptosis by inducing catastrophic mitochondrial dysfunction, modulating intracellular reactive oxygen species (ROS) balances, and activating the classical intrinsic caspase cascade. Many AMPs dictate cancer cell fate by driving localized oxidative stress; while baseline ROS levels can support malignant proliferation via survival pathways, exceeding the tumor's antioxidant capacity paradoxically triggers a pro-apoptotic shift. Several studies demonstrate that target-specific agents induce an overproduction of mitochondrial ROS, causing immediate outer membrane depolarization and triggering downstream apoptotic cascades. For example, lycopene lowers abnormal intracellular ROS levels to alter mitochondrial membrane potential in pancreatic cancer lines, driving caspase-3 activation and elevating the pro-apoptotic Bax to anti-apoptotic Bcl-2 ratio [92]. Conversely, agents like bufalin induce direct ROS-dependent translocation of Bax to the mitochondria, causing a rapid permeability transition, while dihydroartemisinin (DHA) accelerates ROS accumulation to force cytochrome c release and the subsequent activation of caspases-3 and -9 in lung adenocarcinoma models [93, 94].

The mandatory role of this oxidative stress is confirmed by antioxidant rescue assays, where the co-administration of N-acetylcysteine (NAC) completely attenuates mitochondrial injury, verifying that ROS generation is both necessary and sufficient to initiate this programmed death pathway [93, 95]. Upon the loss of mitochondrial outer membrane integrity, the sudden release of internal cytochrome c into the cytosol prompts the assembly of the apoptosome, which activates initiator caspase-9 to drive downstream effector caspases like caspase-3. AMPs and related compounds have been engineered to trigger these events with high efficiency. For instance, the thioredoxin reductase inhibitor auranofin induces mitochondrial permeabilization and cytochrome c leakage in hepatocellular carcinoma models, an effect driven by ROS accumulation that can be entirely reversed via pan-caspase inhibition [96].

This targeted protein modulation is well illustrated by specialized AMPs such as myristoylated CM4, which selectively localizes to the mitochondria of breast cancer lines to drive membrane potential collapse, cytochrome c translocation, and caspase activation [76]. Similarly, in non-small cell lung carcinoma models, teroxirone forces functional p53 accumulation, ROS generation, and intrinsic pathway activation [95]. These processes are strictly regulated by the Bcl-2 family of proteins, where an elevated Bax/Bcl-2 ratio favors permeabilization; this mechanism is shared by alpha-lipoic acid, which suppresses Bcl-2 expressions via ROS-dependent signaling in lung cancer lines, while upstream initiator caspase-2 networks bridge localized oxidative stress and p53 accumulation to execute clean tumor clearance [92, 97, 98].

4.3 Necrosis and Direct Cytotoxicity

Antimicrobial peptides contribute to cancer eradication not only by initiating programmed apoptosis but also by executing rapid necrosis and direct, non-apoptotic cytotoxicity. These alternative pathways involve the physical destruction of the plasma membrane, a complete loss of cellular integrity, and immediate lysis, offering a critical clinical tool to eliminate highly aggressive tumor sub-populations that have developed resistance to traditional caspase-dependent apoptotic signaling. Several AMPs induce a necrotic phenotype characterized by rapid cellular swelling, organelle rupture, and irreversible membrane permeabilization rather than the orderly disassembly seen in apoptosis. This is clearly demonstrated by the PFR peptide, a specialized derivative of human lactoferricin, which exerts powerful cytotoxicity against leukemia cell models by driving primary necrosis. This peptide triggers extensive membrane lesions, marked by massive intracellular propidium iodide uptake, rapid lactate dehydrogenase (LDH) release, and a sudden influx of intracellular calcium. Crucially, PFR treatment does not induce chromatin condensation, caspase activation, or the upregulation of pro-apoptotic Bcl-2 family markers, confirming necrosis as its absolute killing mechanism alongside a favorable safety profile in vivo [99].

Similarly, the cationic peptide KT2 introduces immediate structural alterations across the plasma membrane of human HCT 116 colon cancer lines. Atomic force microscopy has verified that KT2 treatment produces extensive physical defects and lipid scrambling; while the peptide can induce secondary apoptotic features like nuclear condensation over extended exposures, its primary cytotoxic profile relies on direct membrane disruption coupled with the simultaneous inhibition of survival-linked autophagy pathways [80]. Depending on the localized concentration and cellular energy availability, AMPs can initiate a blended cell death spectrum occasionally termed necrapoptosis, where necrotic, apoptotic, and autophagic hallmarks coexist. Physically, necrotic lysis occurs when cellular adenosine triphosphate (ATP) pools are severely depleted by the peptide's membrane-disruptive actions, whereas programmed apoptosis follows if a baseline level of ATP is preserved [100]. Furthermore, this direct cytotoxicity can be amplified by forcing lysosomal membrane permeabilization; combining membrane-active peptides with agents that disrupt vacuolar proton pumps prompts an accumulation of dysfunctional autolysosomes, accelerating necrotic collapse [101]. This multi-modal killing capacity grants AMPs a major therapeutic advantage, allowing them to bypass typical multi-drug resistance phenotypes and systematically eliminate heterogeneous, apoptosis-refractory solid tumors [85, 102].

4.4 Inhibition of DNA, RNA, and Protein Synthesis

Beyond their primary membrane-disruptive capabilities, antimicrobial peptides exert potent anticancer activity by translocating into the cytoplasm to inhibit the synthesis of vital intracellular macromolecules, including DNA, RNA, and proteins. This multi-pronged targeting strategy severely impairs foundational cellular processes within the malignant cell, driving selective cytotoxicity while significantly lowering the statistical probability of the tumor developing acquired resistance. Upon crossing the lipid bilayer, several intracellular-targeting AMPs bypass simple lysis to bind directly to internal components necessary for replication, transcription, and translation. A comprehensive structural analysis reveals that specialized peptide families—most notably pyrrhocoricin, drosocin, apidecin, and Bac7—bind with high affinity to essential molecular chaperones like DnaK and GroEL, disrupting cellular protein homeostasis. Concurrently, these peptides can physically intercalate or bind to DNA and RNA strands, blocking polymerases to halt transcription and downstream translation cascades [103, 104]. For example, the amphipathic peptide melittin permeabilizes the target membrane to reach the cytoplasm, where it directly binds to nucleic acid structures to arrest macromolecular biosynthesis, a dual lytic-biosynthetic block that represents a powerful model for precision oncology design [105].

Additionally, certain AMPs induce the rapid aggregation and compaction of intracellular nucleic acids, disrupting the liquid-liquid phase transitions mandatory for gene expression. Peptides identified through machine learning architectures display a strong propensity to form condensed, liquid-like complexes with cellular DNA and RNA, completely arresting transcription factors. This mechanism is supported by aggregation-prone model sequences like Oct-P2, which can clump plasmid structures to freeze macromolecular assembly, highlighting an intracellular inhibitory potential that operates independently of membrane lysis [106, 107]. Furthermore, proline-rich AMPs target the ribosomal machinery itself, binding within the polypeptide exit tunnel of the ribosome to halt translation elongation. This ribosomal block is complemented by the targeted inactivation of heat shock proteins required for protein folding, inducing catastrophic proteotoxic stress and misfolding cascades [108]. Proteomic profiling of peptide-treated cells confirms wide-scale disruptions across energy metabolism, DNA repair pathways, and translational networks, proving that AMPs systematically undermine the metabolic machinery required for tumor growth and division [109].

4.5 Disruption of Cytoskeletal Organization

The eukaryotic cytoskeleton—composed of an intricate network of actin filaments, microtubules, and intermediate filaments—is essential for maintaining mechanical shape, enabling mitotic division, driving intracellular trafficking, and facilitating cell motility. In malignant cells, particularly during progression and metastasis, extensive cytoskeletal reorganization drives the epithelial-to-mesenchymal transition (EMT), maximizing invasion and migration pathways. Targeting these structural dynamics represents a highly effective therapeutic strategy, and studies confirm that disrupting cytoskeletal architecture paralyzes cancer cell mobility. Actin filaments are primarily responsible for the mechanical elasticity and viscoelastic properties of the cell; destabilizing these microfilaments causes up to an 85% reduction in cellular elasticity and a 79% drop in viscosity, demonstrating that actin plays a dominant role over microtubules in regulating the physical integrity of the tumor cell [110]. Microtubules, while contributing less to baseline elasticity, are

mandatory for mitotic spindle assembly, intracellular transport, and cell polarity. Drugs that modulate these structures drastically alter the cell's bioelectrical signature; for example, the microtubule destabilizer Mebendazole (MBZ) drops the total electrical resistance of breast cancer cells, whereas the stabilizer Paclitaxel (PTX) elevates it, mapping distinct electrical indicators for cytoskeletal disruption [111]. This structural regulation is further supported by tumor suppressors like merlin, which promotes tubulin polymerization; a loss of merlin leads to the structural disorganization characteristic of aggressive schwannomas [112].Treatments that target these structural polymers severely impair metastatic cell motility. Alternating electric fields, known as Tumor Treating Fields (TTFields), disrupt both microtubule assembly and actin polarization, activating the GEF-H1/RhoA/ROCK signaling axis to alter focal adhesion layouts and halt directional migration [113].

Similarly, natural triterpenoids like lupeol reduce the formation of cellular stress fibers by activating actin-depolymerizing factors such as cofilin, suppressing haptotaxis and metastatic invasion without altering microtubule networks [114]. This structural grid is further stabilized by intermediate filaments like vimentin, which cross-talks directly with microtubules to prevent premature depolymerization and maintain cellular mechanics [115]. Furthermore, when cancer cells enter a senescent state, they exhibit widespread cytoskeletal remodeling characterized by elevated microtubule acetylation and a reduction in regulatory kinases like Rock1, which effectively paralyzes migratory capacity, offering an instructive blueprint for designing peptides that target the structural mechanics of the cell [116].

4.6 Anti-Angiogenic Activity of Agents in Cancer Treatment

Anti-angiogenic therapy represents a cornerstone of modern oncological care because solid tumor growth and subsequent systemic metastasis are entirely dependent on the neovascularization of new blood vessels. To overcome acquired resistance to classical vascular endothelial growth factor (VEGF) blockers, multi-targeted approaches focusing on alternative signaling axes have been widely explored. For instance, ferulic acid functions as a novel inhibitor of fibroblast growth factor receptor 1 (FGFR1), successfully suppressing angiogenesis by blocking the downstream FGFR1-mediated phosphatidylinositol 3-kinase (PI3K)-Akt signaling cascade. This compound halts endothelial cell proliferation, migration, and functional tube assembly, preventing microvessel sprouting ex vivo and attenuating tumor growth in vivo within melanoma xenograft models [117]. Similarly, HMG-CoA reductase inhibitors, commonly known as statins, display dose-dependent anti-angiogenic activity at micromolar concentrations; they inhibit endothelial migration, downregulate autocrine VEGF synthesis, and force apoptosis across proliferating vessel walls, serving as effective clinical adjuvants [118].

A major challenge in anti-angiogenic care is the emergence of therapy-induced resistance, which is largely driven by bone marrow-derived myeloid cells that infiltrate the tumor microenvironment under hypoxic conditions. Hypoxia-inducible factors (HIFs) coordinate this response, driving alternative vessel growth and immune evasion to bypass singular VEGF blocks [119]. To resolve this redundancy, contemporary strategies deploy multi-targeted inhibitors that simultaneously block parallel signaling axes, such as the PDGF/PDGFR and FGF/FGFR pathways, preventing tumor escape [120]. Furthermore, integrin alpha-v-beta-3, which is highly expressed on activated endothelial surfaces and malignant cells, serves as a vital regulator of neovascularization and metastasis. Target validation using monoclonal antibodies like MEDI-522, cyclic peptides like Cilengitide, or specialized siRNA silencers demonstrates a profound suppression of tumor growth, especially when paired with conventional radiotherapies [121].

This targeting efficiency is advanced by novel nanotechnology platforms; for example, the htsFLT01/MiRGD fusion protein nanocomplex downregulates VEGF, VEGFR, and cluster of differentiation 31 (CD31) expressions to restrict vascular density and induce widespread tumor apoptosis [122]. Finally, targeting apelin—a key ligand involved in vessel maturation and microenvironmental remodeling—prevents resistance to receptor tyrosine kinase inhibitors, normalizes the chaotic tumor vasculature, and suppresses metastatic pathways in both mammary and lung cancer models [123].

4.7 Immunomodulatory Effects and Tumor Microenvironment Regulation
Antimicrobial peptides do not rely solely on direct physical cytotoxicity; they also function as vital modulators of the host immune response and regulators of the immunosuppressive tumor microenvironment (TME). Their multi-functional attributes allow them to seamlessly bridge innate and adaptive immunity, organize localized inflammatory cascades, and remodel the TME into an immune-permissive zone that potentiates antitumor clearance. The baseline cationic and amphipathic architecture of AMPs allows them to target malignant cells while simultaneously recruiting and activating innate immune responders, including neutrophils, monocytes, dendritic cells, T-lymphocytes, and mast cells [22, 124]. Furthermore, AMPs indirectly enhance adaptive immunity by activating B-lymphocyte networks and promoting antigen-specific humoral and cellular memory, making them excellent adjuvant candidates for anti-cancer vaccine development [124].

Within the solid tumor, the TME is typically characterized by a dense network of immunosuppressive cells, including tumor-associated macrophages (TAMs), microglia, and myeloid-derived suppressor cells (MDSCs), which secrete inhibitory cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) to paralyze cytotoxic T cells. Therapeutic strategies that utilize AMP pathways can actively repolarize these TAMs from a pro-tumor M2 phenotype to an antitumor M1 phenotype, deplete MDSCs, and activate natural killer (NK) cells to restore immune surveillance [125]. Concurrently, AMPs can interact with innate pattern-recognition receptors, such as Toll-like receptors (TLRs), to modulate the highly suppressive activity of regulatory T cells (Tregs), which frequently correlate with poor clinical prognoses [126]. This immune regulation is tightly controlled by endogenous cellular cues; for example, the forkhead box O (FOXO) transcription factor regulates basal AMP gene expression independently of classical infectious pathways to maintain background tissue homeostasis without inducing excessive autoimmunity [127].

Similarly, Vitamin D3 functions as a major systemic regulator of AMP transcription, controlling cathelicidin levels across mucosal boundaries to direct immune cell recruitment and tissue repair [128, 129]. This neuroendocrine-immune axis is further supported by AMPs secreted from the chromaffin cells of the adrenal medulla, which integrate systemic stress responses with frontline innate surveillance [130]. Finally, advanced combinational therapies that pair engineered AMPs with synthetic immune agonists targeting TLR9, STING, or RIG-I pathways show great success in activating antigen-presenting cells, driving robust tumor regression across preclinical models by coordinating both arms of the immune system within the TME [131].

Table 4 | Therapeutic interventions targeting cytoskeletal dynamics and tumour angiogenesis.

Target System / Component	Therapeutic Agent or Context	Primary Biophysical Mechanism	Resulting Impact on Tumor Cells	References
Actin Filaments	Lupeol / Cytochalasin D	Destabilizes microfilament assembly; activates cofilin factoring.	Drops cellular elasticity and viscosity; halts metastatic invasion.	[110, 114]
Microtubules	Mebendazole / Paclitaxel	Modulates tubulin polymerization; alters bioelectrical resistance.	Arrests mitotic spindle formation; triggers cell cycle blocks.	[111, 112]
Cytoskeletal Dynamics	Tumor Treating Fields (TTFields)	Applies alternating electric fields to disrupt polymer alignment.	Disrupts cell polarity; inhibits directional migration.	[113]

Intermediate Filaments	Vimentin Networks	Interacts with microtubules to prevent depolymerization cascades.	Preserves structural mechanics; represents a vulnerability block.	[115]
FGFR1 Signaling	Ferulic Acid	Inhibits FGFR1-mediated PI3K-Akt phosphorylation.	Arrests endothelial migration and microvessel sprouting.	[117]
Angiogenic Axis	Statins (High Dose)	Blocks HMG-CoA reductase; downregulates autocrine VEGF synthesis.	Inhibits endothelial proliferation; induces vessel wall apoptosis.	[118]
Integrin Core	αvβ3 Antagonists	Blocks activated endothelial and tumor cell integrin signaling.	Suppresses neovascularization and distant metastasis.	[111, 121]
Vascular Nanocomplex	htsFLT01/ MiRGD System	Downregulates VEGF, VEGFR, and CD31 expressions.	Restricts microvessel density; induces tumor apoptosis.	[122]
Apelin Pathway	Apelin Inhibitors	Normalizes chaotic tumor vasculature configurations.	Reverses resistance to tyrosine kinase blockers; curbs metastasis.	[123]

Representative therapeutic approaches targeting cytoskeletal organization and angiogenic signalling pathways, together with their molecular mechanisms and biological effects on tumour progression.

4.8 Induction of Immunogenic Cell Death by Antimicrobial Peptides in Cancer Therapy

Immunogenic cell death (ICD) represents a unique and highly regulated form of cancer cell demise that, unlike immunologically silent or tolerogenic apoptosis, actively stimulates the host's immune system to recognize and systematically eradicate tumor cells. Antimicrobial peptides (AMPs), extending far beyond their role as direct cytotoxic agents, have emerged as potent inducers of ICD. By doing so, they seamlessly bridge innate physical cytotoxicity with adaptive immune activation to enhance long-term antitumor immunity. The primary biophysical mechanisms of ICD induction are initiated when AMPs disrupt the cancer cell plasma membrane, triggering apoptosis, necrosis, or mixed necrapoptotic cell death modalities. This disruption is accompanied by severe mitochondrial dysfunction, intense endoplasmic reticulum (ER) stress, and a massive accumulation of intracellular reactive oxygen species (ROS). These synchronized cellular stress signals activate downstream ICD pathways, resulting in the cell-surface exposure or extracellular release of damage-associated molecular patterns (DAMPs), which serve as critical immunostimulatory signals that alert and activate host immune surveillance [132, 133].

The canonical DAMPs associated with AMP-induced ICD cascades include the pre-apoptotic translocation of calreticulin (CRT) to the outer leaflet of the cell surface, the active secretion of adenosine triphosphate (ATP), and the passive leakage of high mobility group box 1 (HMGB1) protein, alongside key heat shock proteins like HSP70 and HSP90. Once released into the extracellular milieu, these specialized molecules facilitate the rapid chemotactic recruitment and phenotypic maturation of dendritic cells (DCs), drastically improving the phagocytosis of dying tumor fragments and ensuring highly efficient tumor-associated antigen presentation [134, 135]. Following this DAMP emission, immature DCs recognize these danger signals through specific pattern recognition receptors. Mature DCs then process and present the captured tumor antigens to cytotoxic T lymphocytes (CTLs), initiating a robust, antigen-specific adaptive immune response. This signaling cascade not only drives acute, localized tumor cell clearance but also promotes the formation of protective immune memory, shielding the host against subsequent metastatic relapse [132, 133].

Both synthetic and natural AMPs designed to target mitochondrial membranes accelerate this cascade by amplifying intracellular ROS and ER stress. For instance, PAMAM-based polymeric ICD inducers generate strong oxidative stress fields, driving widespread dendritic cell maturation and significant tumor growth suppression in preclinical models, an effect that can be further enhanced when paired with immune checkpoint blockade [136]. Furthermore, AMP-induced ICD can be synergistically augmented when combined with other modern immunotherapeutic agents, such as programmed cell death protein 1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitors, working together to overcome tumor-mediated immune evasion and reverse microenvironmental immunosuppression [137, 138]. Several distinct examples highlight the clinical potential of ICD induction via AMPs and related membrane-active agents. For example, shikonin, a natural product derivative, induces robust ICD characterized by the elevated expression of all major canonical DAMPs, which enhances the efficacy of dendritic cell vaccines and drives potent T-helper 1 (Th1) and Th17 immune responses in vivo [139]. Similarly, near-infrared photoimmunotherapy (NIR-PIT), which acts as a powerful adjunctive modality alongside AMP systems, produces rapid physical membrane lesions and immediate DAMP exposure to accelerate antitumor immunity [135]. This multi-pronged approach is also seen in combinatorial strategies that pair ROS-mediated ER stress with specific pyroptosis inducers to enhance ICD markers and tumor-specific T-cell activation within aggressive multiple myeloma models [140]. Additionally, fluorinated mitochondria-targeting helical polypeptides have been engineered to disrupt internal mitochondrial membranes; this action produces a wave of ROS-mediated ER stress and subsequent ICD that synergizes with PD-L1 blockade to drive complete tumor regression and systematically prevent distant metastasis [138].

Ultimately, the capacity of AMPs to initiate immunogenic cell death provides a powerful dual oncology modality: executing immediate, direct tumor cell killing while simultaneously activating the host immune system to achieve long-lasting antitumor surveillance. This cross-functional property makes AMPs promising candidates when deployed either as targeted monotherapies or as molecular adjuvants designed to maximize the therapeutic durability of existing immune checkpoint inhibitors. Moving forward, emerging synthetic polymers and engineered AMP derivatives that efficiently trigger these ICD pathways hold particular clinical promise due to their highly tunable biophysical properties, allowing for precision targeting, enhanced immunogenicity, and optimal synergistic potential with modern immunomodulatory agents [136].

5. Major Types of Antimicrobial Peptides Used in Cancer Research

Among the various classes of antimicrobial peptides (AMPs) studied for their anticancer potential, human-derived antimicrobial peptides constitute a significant category due to their natural presence in innate immunity and inherent biocompatibility. These peptides have been extensively explored as novel anticancer agents either as monotherapies or in combination with established chemotherapeutics.

5.1 Human-Derived Antimicrobial Peptides

Human-derived AMPs originate directly from the frontline innate immune defenses of the host and primarily include families such as defensins and cathelicidins, both of which display multifunctional properties beyond basic microbial killing, notably immunomodulatory and anticancer activities. Structurally, these human-derived sequences are generally short, positively charged, and amphipathic. This structural arrangement allows them to selectively interact with the negatively charged phospholipids exposed on the outer leaflets of cancer cell membranes, leading to localized membrane disruption, apoptosis induction, and the targeted inhibition of intracellular signaling pathways relevant for tumor growth [20, 24]. This

selective binding drives a preferential cytotoxicity toward tumor cell lines while sparing healthy mammalian tissue, a threshold attributed to major differences in membrane composition, surface charge density, and lipid fluidity between malignant and normal cells.

Beyond asserting direct cytotoxic effects, human AMPs actively remodel the tumor microenvironment by directing immune cell recruitment, modulating cytokine production profiles, and suppressing tumor angiogenesis, supporting their integration into comprehensive anticancer strategies [24, 141]. Despite these natural advantages, developing wild-type human AMPs into clinical therapies faces major bottlenecks regarding physiological stability, low bioavailability, and potential systemic toxicity, necessitating advanced bioengineering interventions. Modifications such as recombinant fusion with human serum albumin or antibody Fc domains, along with post-synthetic chemical modifications like targeted lipidation, have shown great potential in expanding peptide half-life and target specificity [20]. Currently, human-derived AMPs continue to advance through preclinical pipelines, with several candidates undergoing intensive evaluation for their anticancer efficacy, immune-checkpoint modulation potential, and combinatorial use with conventional chemotherapies. Their intrinsic role in host defense offers distinct genetic advantages regarding low immunogenicity and superior patient tolerability compared to non-human peptide sequences [27, 142].

5.2 Animal-Derived Antimicrobial Peptides

Animal-derived antimicrobial peptides, particularly those sourced from venomous and non-venomous species, represent a potent repository of bioactive molecules under investigation for oncology applications. These peptides, evolved over millennia as innate defensive effectors, are highly capable of selectively targeting cancer cell membranes and disrupting tumor-associated pathways. Insects provide one of the broadest and most diverse repertoires of these molecules. Insect-derived AMPs have demonstrated powerful antimicrobial and antitumor activities in vitro, though their therapeutic translation faces strict barriers, including potential cytotoxicity, systemic immunogenicity, allergenicity, and high production costs. Current bioengineering advances, such as the design of synthetic peptide analogs and optimized recombinant expression within insect cell systems or plant tissues, are being deployed to overcome these scale-up barriers, positioning insect AMPs as excellent structural templates for rational peptide design [143]. Concurrently, venom-derived peptides isolated from animals such as scorpions, wasps, and honey bees have attracted substantial research attention due to their ability to selectively eliminate cancer cells while maintaining low toxicity toward normal tissues. Scorpion venom peptides, especially those derived from Asian species, interact directly with eukaryotic ion channels—including voltage-gated sodium, potassium, and calcium channels—thereby paralyzing cancer cell proliferation and inducing programmed apoptosis.

Although identifying and isolating these sequences presents challenges regarding target specificity and raw venom toxicity, ongoing research utilizes structural modifications to improve their therapeutic index and drive clinical translation [144, 145]. Animal venoms comprise complex biochemical mixtures containing peptides, enzymes, and specialized toxins that serve as highly efficient natural templates for drug development. These compounds systematically disrupt cancer progression by forcing protein synthesis inhibition, angiogenesis disruption, and apoptosis induction, making them promising leads for cost-effective cancer therapies that combine membrane-lytic mechanisms with host immunomodulation [22, 23, 144].

5.3 Marine-Derived Antimicrobial Peptides

Marine organisms—encompassing diverse phyla such as algae, cyanobacteria, sea sponges, ascidians, tunicates, mollusks, and fish—represent an extraordinarily rich source of AMPs characterized by unique chemical structures and potent anticancer actions. Peptides isolated from marine biomes often incorporate unusual, non-proteinogenic amino acids that contribute heavily to their structural bioactivity and metabolic selectivity against tumor cells. Purified marine-derived peptides and targeted protein hydrolysates have displayed robust antiproliferative, antioxidant, antimicrotubule, and cytotoxic effects against a wide variety of human cancer cell lines, including HeLa, AGS, and DLD-1 models. These marine molecules operate through a diverse mechanical spectrum, including the simultaneous induction of apoptosis and necrosis, the intracellular generation of reactive oxygen species (ROS), severe mitochondrial dysfunction, and direct genomic DNA damage [49, 146].

Fish-derived AMPs, in particular, have demonstrated broad-spectrum anticancer effects in vitro, frequently executing tumor clearance by exploiting cancer-specific oxidative stress vulnerabilities and triggering irreversible cell death. To achieve successful clinical translation, these fish-derived sequences require structural optimization through synthetic design and encapsulation within advanced drug delivery systems to enhance their circulating stability, baseline bioavailability, and tumor-homing precision [49]. Overall, marine-derived AMPs offer unique chemical scaffolds and novel modes of action that significantly expand the contemporary oncology toolbox, especially given their multifaceted bioactivities and relatively lower background toxicity profiles compared to terrestrial counterparts [22].

5.4 Plant-Derived Antimicrobial Peptides

Plant-derived antimicrobial peptides, notably ribosomally synthesized and post-translationally modified peptides (RiPPs), constitute a highly promising source of anticancer agents characterized by remarkable structural diversity and potent cytotoxicity. Plant RiPPs, such as rubipodanin A and mallotumides A-C, display exceptional nanomolar-scale IC50 values against various human cancer cell lines, underscoring their vast therapeutic potential. These specialized peptides can be rapidly identified and optimized by integrating traditional ethnobotanical knowledge frameworks with modern high-throughput genomics and bioinformatics, representing a highly sustainable and scalable avenue for novel anticancer drug discovery [147]. Botany-derived antimicrobial peptides are frequently cysteine-rich molecules that form an integral part of the plant kingdom's innate immune system.

These peptides exhibit powerful cross-kingdom anticancer properties, including the simultaneous suppression of tumor cell proliferation and co-occurring viral infections in human health contexts. Their broad spectrum of activity, reliance on multiple parallel mechanisms of action, and low host cytotoxicity make them ideal structural templates for rational drug design targeting solid tumors. Their foundational biological properties, characterized by immediate membrane disruption coupled with targeted interactions against vital intracellular components, highlight their growing utility in the development of novel anticancer therapeutics [148].

5.5 Bacterial-Derived Antimicrobial Peptides

Bacterial-derived antimicrobial peptides, commonly categorized as bacteriocins, are short, typically cationic, and amphiphilic peptides produced ribosomally by both Gram-positive and Gram-negative bacterial strains. These peptides serve as potent antimicrobial weapons that bacteria utilize to eliminate competing microorganisms within their ecological niches. Their high targeting specificity and unique modes of action make them highly attractive alternatives for addressing multi-drug resistance challenges. Bacteriocins typically exert their primary activity by binding to and disrupting the cellular membranes of targeted bacterial cells, leading to rapid pore formation and cell death. Unlike traditional broad-spectrum antibiotics, many bacteriocins possess a narrow spectrum of activity, allowing for the targeted elimination of specific bacterial pathogens with minimal disruptive impact on the surrounding commensal flora, a high specificity that minimizes dysbiosis and the gastrointestinal side effects associated with classic anti-infective therapies [149].

In addition to their primary antibacterial mechanics, bacterial AMPs have demonstrated positive therapeutic effects on the human body, including potent immunomodulatory properties that can be exploited in oncology. However, significant developmental challenges remain, particularly regarding the optimization of peptide metabolic stability, industrial production scale-up, and targeted delivery methods necessary to translate bacteriocins into standard clinical practice. Despite these current limitations, ongoing research continues to explore their dual role as alternative monotherapies or as potent molecular adjuvants to conventional therapeutics, especially when designing protocols to target multidrug-resistant bacterial strains within the tumor microenvironment [149].

5.6 Synthetic and Modified Antimicrobial Peptides

Synthetic and modified antimicrobial peptides represent a rapidly expanding frontier in design, explicitly engineered to overcome the natural limitations of wild-type sequences, such as poor metabolic stability, short circulating half-lives, rapid proteolytic degradation, and off-target cytotoxicity. Critical advances in solid-phase chemical synthesis, bioinformatics, and computational peptide engineering now allow for the de novo design of novel peptides or the strategic modification of natural sequences to maximize therapeutic efficacy while minimizing structural drawbacks. Employed methodologies include the systematic introduction of non-natural amino acids, backbone cyclization, lipidation, PEGylation, and the precise incorporation of structural motifs designed to promote self-assembly into smart nanoparticles or nanofibers, which vastly improve structural stability and localized biological activity [16].

These self-assembled AMP architectures exhibit several major advantages over their monomeric counterparts, including significantly higher thermal and enzymatic stability, enhanced systemic biocompatibility, and potentiated anticancer efficacy. These advanced nanostructured configurations—including spherical nanoparticles, nanorods, and aligned nanofibers—provide reliable platforms for controlled drug delivery and sustained, localized activity, often enabling reduced systemic toxicity and improved tumor targeting [16]. Moreover, synthetic AMPs are designed to specifically target the unique biophysical traits of cancer cell membranes, such as exposed negatively charged phospholipids, or to induce immunogenic cell death (ICD), effectively combining direct mechanical cytotoxicity with systemic host immune activation.

Certain synthetic derivatives, most notably the oncolytic peptide LTX-315, have shown immense promise across preclinical and clinical trials, demonstrating a robust ability to force tumor antigen release and rapidly modulate the immunosuppressive tumor microenvironment [48]. The clinical translation of synthetic AMPs remains an active area of development, with current efforts focusing on optimizing pharmacokinetics, eliminating off-target hemolytic effects, and enhancing overall potency via combination regimes with established chemotherapies [14, 150].

Table 5 | Major classes of antimicrobial peptides investigated for cancer therapy.

Peptide Classification	Primary Biological Source / Engineering Approach	Key Biophysical Features and Advantages	Primary Developmental Challenges	Core References
Human-Derived AMPs	Endogenous innate immune defenses (e.g., Defensins, Cathelicidins).	High biocompatibility; multi-functional immunomodulation; low background immunogenicity.	Low in vivo half-life; susceptibility to serum proteases; optimization costs.	[20, 24, 141, 142]
Animal-Derived AMPs	Vertebrate and invertebrate defense secretions (e.g., Insect toxins, Scorpion venom).	High lytic potency; ion-channel modulation capabilities; unique amino acid templates.	Off-target cytotoxicity; systemic allergenicity; scaling and extraction purity.	[22, 23, 143, 144, 145]
Marine-Derived AMPs	Marine organisms (e.g., Algae, Sponges, Tunicates, Fish).	Incorporates unusual amino acids; unique chemical scaffolds; low baseline mammalian toxicity.	High structural complexity; isolation challenges; delivery optimization requirements.	[22, 49, 146]
Plant-Derived AMPs	Botany immune systems (e.g., Cysteine-rich RiPPs, Rubipodanin A).	High structural stability; nanomolar-scale IC50 values; cross-kingdom therapeutic activity.	Complex extraction procedures; optimization of bioavailability profiles.	[147, 148]
Bacterial-Derived AMPs	Ribosomally synthesized bacteriocins (Gram-positive/ Gram-negative bacteria).	Ultra-narrow spectrum specificity; potent against multi-drug resistant strains; low dysbiosis.	Industrial scale-up bottlenecks; formulation stability; targeted in vivo delivery.	[149]
Synthetic & Modified AMPs	De novo computational design and chemical modification (e.g., LTX-315, PEGylation).	Tunable pharmacokinetics; high proteolytic resistance; enables advanced self-assembled nanoformulations.	Complex optimization of systemic toxicity; rigorous regulatory and clinical validation path.	[14, 16, 48, 150]

Representative antimicrobial peptide families classified according to their biological origin, structural characteristics, anticancer mechanisms, and therapeutic potential.

6. Antimicrobial Peptides Against Different Cancer Types

Antimicrobial peptides (AMPs) have emerged as promising anticancer agents due to their selective cytotoxicity toward tumor cells, unique immunomodulatory properties, and distinct ability to physically affect the tumor microenvironment. Their structural and functional versatility allows for targeted application across a wide spectrum of malignancies, with each cancer type demonstrating unique biophysical interactions and therapeutic profiles.

6.1 Breast Cancer

AMPs exhibit potent anticancer activity against breast cancer cell lines by inducing targeted membrane disruption and destroying internal intracellular components while leaving healthy host cells undamaged. Their baseline cationic charge and amphipathic alpha-helical conformation facilitate highly selective electrostatic docking onto breast tumor surfaces, driving immediate apoptosis and successfully suppressing downstream metastatic pathways. Crucially, several engineered AMPs have demonstrated a robust capacity to overcome multidrug resistance phenotypes against conventional chemotherapeutic drugs in refractory breast cancer models, highlighting their clinical potential as powerful molecular adjuvants or standalone alternative treatments [22, 24].

6.2 Lung Cancer

In lung cancer therapeutics, AMPs execute selective cytotoxicity primarily through direct plasma membrane disruption and targeted mitochondrial localization. This localization leads to massive intracellular reactive oxygen species (ROS) generation, forcing outer membrane potential collapse and triggering programmed cell death via the intrinsic apoptotic cascade. Beyond this mechanical cytotoxicity, these peptides actively stimulate host immune responses within the lung tumor microenvironment, promoting

localized dendritic cell maturation and cytotoxic T-cell activation to enhance long-term antitumor immunity, particularly when targeting aggressive, chemoresistant, and highly metastatic lung cancer variants [22, 151].

6.3 Colorectal Cancer

AMPs designed against colorectal cancer disrupt tumor cell membranes while simultaneously interfering with baseline cellular metabolism. They induce immunogenic cell death (ICD) to force the exposure of critical surface danger signals, effectively remodeling the local immune milieu to halt colorectal tumor proliferation and distant metastasis. Furthermore, specific bacterial and synthetic AMP configurations have been shown to work in synergy with conventional frontline chemotherapies and modern immune checkpoint inhibitors, vastly improving therapeutic durability and outcomes in advanced colorectal cancer models [24, 152].

6.4 Prostate Cancer

AMPs targeting prostate cancer cell lines demonstrate high clinical efficacy through rapid, direct membrane lysis and the induction of apoptosis via the targeted depolarization of internal organelles like the mitochondria. Their charge-dependent selectivity ensures that this lytic cytotoxicity avoids damaging normal, zwitterionic prostate tissue boundaries. Additionally, these peptides are capable of actively modulating and reversing the severe immune suppression frequently observed within prostate tumor microenvironments, potentially enhancing the clinical success rates of co-administered immunotherapies [22, 151].

6.5 Liver Cancer

In hepatocellular carcinoma and related liver malignancies, AMPs successfully inhibit tumor growth and progression via immediate membrane permeabilization and the disruption of downstream oncogenic signaling networks. Their capacity to actively modulate the chronic, inflammatory tumor microenvironment of the liver while simultaneously forcing immunogenic cancer cell death supports their emerging dual role in both direct cytotoxic protocols and advanced, immune-based liver cancer therapies [24, 153].

6.6 Melanoma

AMPs elicit exceptional anticancer effects against melanoma through a combination of direct cytolytic activity and the immediate activation of adaptive immune responses. Several specialized peptide sequences promote localized dendritic cell activation and robust cytotoxic T-lymphocyte (CTL) responses, driving significant tumor regression in vivo. Moreover, combinational regimes pairing membrane-active AMPs with synthetic immune checkpoint inhibitors have shown enhanced therapeutic synergy in preclinical melanoma models [131, 151].

6.7 Brain Tumors and Glioblastoma

Glioblastoma multiforme is notorious for its highly immunosuppressive tumor microenvironment, but it exhibits unique susceptibility to specialized AMP-based interventions designed to disrupt or reprogram tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs). These peptides modulate frontline innate immune responses while directly executing tumor cell lysis. Advanced nanotechnology approaches that incorporate these AMP sequences into innate immune agonist nanoparticles have yielded exceptional antitumor immunity and significant tumor burden reduction across blood-brain barrier models [125, 131].

6.8 Hematological Malignancies

AMPs have been intensively investigated across various liquid blood cancers, including multiple leukemia and lymphoma lines, demonstrating a powerful capacity to initiate immunogenic cell death and trigger programmed apoptosis in malignant hematopoietic cells. By stimulating the rapid activation of circulating immune effector cells, these peptides offer a reliable mechanical route to systematically overcome the intrinsic immune evasion mechanisms characteristic of hematological malignancies [24, 151].

7. Antimicrobial Peptides as Drug Delivery Tools

Antimicrobial peptides have significantly expanded their clinical role beyond direct anticancer activity to function as highly versatile drug delivery platforms. Their intrinsic biophysical traits, such as deep membrane penetration and target-specific tumor homing, enable a wide variety of delivery strategies designed to maximize therapeutic specificity, eliminate systemic off-target toxicity, and accelerate the intracellular delivery of poorly soluble chemotherapeutic payloads.

7.1 Cell-Penetrating Peptide Function

Cell-penetrating peptides (CPPs) are short, frequently cationic amino acid sequences capable of translocating across biological membranes to ferry diverse molecular cargos directly into the cytoplasm. AMPs engineered with intrinsic CPP functionality facilitate the immediate intracellular delivery of therapeutic payloads—including small-molecule drugs, nucleic acids, and functional proteins—successfully overcoming the low cellular uptake barriers that limit many traditional pharmaceuticals. However, wild-type CPPs generally exhibit non-selective uptake kinetics, partitioning into healthy and malignant cells alike.

To resolve this limitation, CPP sequences are frequently bioengineered to include dual-receptor recognition motifs that prioritize selective tumor homing. For example, the dual-receptor tandem peptide R8-dGR couples an octa-arginine CPP domain with a precise targeting sequence that recognizes overexpressed integrin alpha-v-beta-3 (αvβ3) and neuropilin-1 receptors. This structural combination achieves exceptional glioma cell uptake and deep intratumoral penetration of drug-loaded liposomes, delivering paclitaxel to demonstrate significant tumor suppression and extended survival in vivo [154]. Furthermore, these CPP vectors can be combined with distinct mitochondria-targeting sequences to guide drug payloads to specific subcellular organelles, amplifying reactive oxygen species (ROS)-mediated apoptotic signaling [155].

7.2 Tumor-Targeting Peptide Systems

Beyond basic membrane penetration, tumor-targeting peptide networks confer exceptional therapeutic specificity by binding directly to overexpressed receptors on the cancer cell surface, helping concentrate cytotoxic payloads selectively within the solid tumor mass. Peptides that recognize integrin αvβ3 complexes or other tumor-associated biomarker signatures enhance delivery efficiency by facilitating rapid, receptor-mediated endocytosis. Knottin peptide-drug conjugates (KDCs) exemplify this precision approach, selectively ferrying chemotherapeutic payloads like gemcitabine to integrin-expressing tumor targets with high binding affinity and controlled intracellular release, resulting in potent antiproliferative outcomes even within drug-resistant tumor sub-populations [156].

Similarly, diketopiperazine-scaffolded peptide networks incorporating integrin-binding RGD motifs conjugated directly to cell-penetrating sequences have been developed; these systems execute targeted cytotoxicity against αvβ3-positive cancer lines via a multi-step mechanism where precise receptor docking strictly precedes CPP-mediated internalization [157]. Additionally, modifying liposomal surfaces with tumor-targeting ligands like transferrin alongside functional CPPs such as the transactivator of transcription (TAT) peptide creates dual-ligand delivery systems that selectively penetrate melanoma cells, optimizing intracellular chemotherapy accumulation and driving synergistic cytotoxicity [158].

7.3 Peptide-Drug Conjugates

Peptide-drug conjugates (PDCs) covalently couple therapeutic or targeting peptides to potent cytotoxic agents via carefully engineered cleavable or stable linkers, enabling precise drug deposition within the tumor. PDCs combine several major clinical advantages over traditional antibody-drug conjugates (ADCs), including a significantly smaller molecular size for superior tissue penetration, streamlined chemical synthesis pathways, and low background immunogenicity. Structurally, PDCs integrate cell-penetrating peptides to drive cargo internalization and cell-targeting

peptides to recognize specific tumor receptors, relying on linkers tailored to undergo rapid cleavage only when exposed to the specific pH or enzymatic conditions of the tumor microenvironment. Notable examples include the FDA-approved radiopharmaceutical lutetium-177 DOTATATE alongside investigational compounds like paclitaxel-Angiopep-2 and LyP-1-doxorubicin conjugates [159, 160]. The primary challenges in contemporary PDC development focus on improving low in vivo plasma stability, avoiding rapid renal clearance caused by their small molecular footprint, and managing the natural heterogeneity of tumor receptor expression; however, they remain a premier modality for delivering toxic payloads with high specificity [161].

7.4 Nanoparticle-Assisted Peptide Delivery

Self-assembling peptides can spontaneously organize into highly ordered supramolecular nanoarchitectures—such as spherical nanoparticles, nanorods, and aligned nanofibers—that serve as protective drug delivery vehicles. These structural nanoframeworks enhance the systemic stability, baseline bioavailability, and target-site concentration of encapsulated chemotherapeutic agents. Furthermore, the intrinsic fluorescence profiles of specific aromatic peptide sequences allow for the real-time optical tracking of drug release kinetics and cellular uptake pathways without requiring external radiolabels. Dipeptide modules, for instance, can self-assemble via coordinated metal-ion complexation to facilitate rapid endosomal escape, accelerating intracellular drug efficacy. These stimuli-responsive peptide nanostructures can be engineered as pH-activated or enzyme-sensitive systems, ensuring controlled payload release strictly within the acidic tumor matrix [162]. Additionally, nanoparticle carriers—including advanced immune agonist nanoparticles that integrate multiple innate immune stimulators alongside tumor-specific targeting peptides—can be deployed to enhance host anticancer immunity alongside coordinated chemotherapy regimens [131].

7.5 Liposome and Hydrogel-Based Delivery Systems

Liposomal platforms modified with both tumor-targeting ligands and functional CPPs provide a versatile, high-capacity system for encapsulating and delivering combination chemotherapy regimes. These dual-ligand liposomes, such as those targeting transferrin receptors while utilizing the TAT cell-penetrating peptide, demonstrate exceptional cellular uptake, deep solid-tumor penetration, and the highly efficient synergistic killing of aggressive melanoma cells when co-loaded with paclitaxel and doxorubicin [158]. Concurrently, supramolecular hydrogels composed of self-assembling peptide-drug conjugates represent an innovative class of self-delivery networks characterized by superior proteolytic stability and excellent cellular uptake kinetics. For example, nanofibrous hydrogels formed by directly conjugating the alkylating agent chlorambucil to specific peptide sequences exhibit prolonged resistance against circulating proteases, accelerated intracellular delivery, and superior in vivo antitumor efficacy, offering a promising, localized platform for combination cancer therapy [163].

7.6 Combination of Antimicrobial Peptides with Chemotherapy Drugs

Combining AMPs with traditional small-molecule chemotherapy agents allows clinicians to exploit powerful biochemical synergies, maximizing overall anticancer efficacy while lowering systemic toxicities. The dual membrane-disruptive and immunomodulatory properties of AMPs can be utilized to physically permeabilize the lipid bilayer, accelerate intracellular drug accumulation, bypass typical multi-drug efflux pumps, and potentiate host immune surveillance against the tumor. For instance, CPP-modified liposomal vectors co-loaded with paclitaxel and doxorubicin achieve a massive increase in tumor cell apoptosis and superior therapeutic outcomes compared to single-agent protocols. Similarly, peptide carriers can be tailored to facilitate targeted mitochondrial delivery of pro-apoptotic agents, augmenting chemotherapy-induced oxidative stress, forcing immediate cytochrome c release, and executing clean tumor clearance [155, 158]. These combinatorial strategies leverage the distinct, parallel mechanisms of AMPs and conventional chemotherapy to maximize tumor cytotoxicity while effectively minimizing off-target side effects.

Table 6 | Advanced drug delivery platforms for antimicrobial peptide-based cancer therapy

Delivery System Strategy	Representative Example / Motif	Primary Intracellular Mechanism	Core Therapeutic Advantage	Key Constraints	Primary References
Cell-Penetrating Peptides	R8-dGR Tandem Sequence	Direct translocation across lipid bilayers via cationic fields.	Overcomes poor cellular uptake; deep tumor penetration.	Non-selective uptake; rapid systemic clearance.	[154, 155]
Tumor-Targeting Systems	Knottin KDCs / RGD Motifs	Binds overexpressed receptors to force endocytosis.	High tumor specificity; minimizes off-target toxicity.	Tumor receptor heterogeneity and variability.	[156, 157, 158]
Peptide-Drug Conjugates	Lutetium-177 DOTATATE	Covalent linking to cytotoxins via bio-cleavable bonds.	High penetration; low immunogenicity; easy synthesis.	Rapid renal clearance; variable in vivo stability.	[159, 160, 161]
Nanoparticle-Assisted Tools	Supramolecular Dipeptides	Spontaneous self-assembly; stimuli-responsive release.	Controlled release kinetics; tracks real-time uptake.	Complex scaling; clinical translation bottlenecks.	[131, 162]
Liposome & Hydrogel Matrix	Dual-ligand TAT-Transferrin	High-capacity lipid encapsulation; proteolytic shielding.	Delivers combination chemotherapies; localized stability.	Manufacturing complexity; in vivo gelation controls.	[158, 163]
Chemotherapy Combination	Co-loaded Paclitaxel-AMPs	Membrane permeabilization coupled with DNA/organelle targets.	Maximizes cytotoxicity; overrides multi-drug resistance.	Demands rigorous dosing and scheduling optimization.	[155, 158]

Representative delivery systems developed to improve the stability, tumour targeting, controlled release, and therapeutic efficacy of antimicrobial peptides in cancer treatment.

8. Advantages of Antimicrobial Peptides in Cancer Therapy

Antimicrobial peptides (AMPs) are gaining widespread recognition as highly promising anticancer agents due to their unique biophysical and biochemical properties that offer distinct advantages over conventional oncological therapies. Their multifunctional mechanisms of action, inherent ability to selectively target malignant cells, and excellent compatibility with combinatorial therapeutic approaches position them as valuable assets in modern precision oncology.

8.1 Selective Toxicity Toward Cancer Cells

One of the most significant clinical advantages of AMPs is their exceptional selectivity for cancer cells while systematically sparing normal, healthy host tissues. This selectivity arises primarily because cancer cell plasma membranes frequently expose negatively charged phospholipids, such as phosphatidylserine, onto their outer leaflets and possess a significantly higher membrane fluidity compared with normal cells. This distinctive surface charge density enables cationic and amphipathic AMPs to preferentially bind and physically disrupt tumor cell membranes via electrostatic interactions. Consequently, AMPs induce targeted cytotoxicity specifically within malignant cell populations, drastically reducing the collateral tissue damage and severe systemic side effects typical of traditional small-molecule chemotherapeutic agents [22, 24].

8.2 Rapid Mechanism of Action

AMPs generally exert their primary anticancer effects by rapidly disrupting cancer cell membranes, leading to swift mechanical cell lysis or the immediate initiation of downstream apoptotic cascades. Because this physical, membrane-lytic mechanism occurs within minutes of exposure, it drastically reduces the available time window for cancer cells to activate standard genetic defense pathways or upregulate multi-drug resistance mechanisms. Furthermore, many AMPs can rapidly penetrate the cell matrix to target internal intracellular organelles or metabolic pathways directly involved in tumor proliferation and survival, substantially increasing their overall therapeutic efficacy and contributing to their ability to counter rapid tumor growth effectively [22, 24].

8.3 Lower Possibility of Drug Resistance

Because AMPs primarily disrupt cell membranes via physical, non-receptor-mediated, and multi-target mechanisms, cancer cells face immense evolutionary difficulty in developing functional resistance compared to traditional drugs that rely on single, specific molecular targets. The extensive biophysical damage inflicted by AMPs across the entire membrane architecture makes single-mutation escape routes highly improbable. Additionally, specific AMP configurations can simultaneously modulate the surrounding tumor microenvironment and host immune responses, further limiting the survival and escape mechanisms available to changing tumors—a critical advantage given that drug resistance remains a principal challenge in clinical oncology [22, 164].

8.4 Potential for Combination Therapy

AMPs are highly versatile agents that can be deployed either as potent monotherapies or synergistically alongside other anticancer drugs to enhance overall clinical outcomes. Their rapid membrane-lytic activity can be exploited to deliberately increase tumor cell permeability, thereby facilitating and improving the intracellular uptake of co-administered conventional chemotherapeutic payloads. Moreover, AMPs can actively sensitize refractory cancer cells to chemotherapy or immunotherapy, effectively overcoming existing drug resistance phenotypes and reducing the necessary clinical dosages of highly toxic agents, which diminishes systemic toxicity. This potential to design custom peptide-drug conjugates and to co-deliver AMPs with conventional small molecules greatly expands contemporary therapeutic strategies [22, 24].

8.5 Ability to Target Both Tumor Cells and Tumor Microenvironment

Beyond asserting direct mechanical cytotoxicity, AMPs can actively modulate the tumor microenvironment (TME) by directing the chemotactic recruitment and phenotypic activation of host immune cells, disrupting tumor-supportive angiogenesis networks, and remodeling the extracellular matrix. Successfully targeting the TME directly addresses and neutralizes tumor-supportive host mechanisms, such as localized immunosuppression and stroma-mediated drug resistance. This dual targeting capability enhances overall antitumor efficacy and may drastically improve long-term treatment outcomes by preventing tumor recurrence, local relapse, and distant metastatic cascades [22, 165, 166].

8.6 Possibility of Structural Modification and Optimization

AMPs offer a highly flexible molecular platform for advanced chemical and structural modifications—including rational amino acid substitutions, backbone cyclization, covalent conjugation with functional nanoparticles or polymers, and custom formulation into smart delivery systems—to enhance their serum stability, bioavailability, and targeting selectivity while eliminating potential background toxicity. Recent advances in automated peptide engineering and nanotechnology facilitate the rapid optimization of AMP properties for human clinical use. For example, conjugating AMPs with protective human serum albumin scaffolds or incorporating targeted lipid modifications significantly improves in vivo pharmacokinetics and systemic tolerance. These highly adaptable features position AMPs as customizable, programmable agents tailored to specific cancer types and patient-specific treatment regimens [167, 168, 169].

9. Limitations and Challenges of Antimicrobial Peptides in Cancer Therapy

Despite their promising anticancer potential, antimicrobial peptides face several significant limitations and biochemical challenges that currently impede their rapid clinical translation. These developmental hurdles span a wide range of issues, from low biological stability within complex physiological fluids to high production complexities and potential systemic safety concerns.

9.1 Toxicity Toward Normal Cells

A primary challenge restricting the clinical deployment of certain wild-type sequences is their residual toxicity toward normal, healthy host cells. Although many AMPs exhibit high selective affinity against cancer cells by targeting negatively charged tumor membranes, specific hydrophobic or highly charged peptides may also non-selectively disrupt the zwitterionic membranes of non-malignant host cells, leading to severe intravascular hemolysis or off-target tissue cytotoxicity. Current mitigation strategies, such as precise molecular modifications, charge tuning, and controlled spatial distribution via protective polymeric carriers, have shown great promise in reducing this systemic toxicity while fully maintaining target anticancer efficacy [170].

9.2 Poor Stability in Biological Fluids

AMPs frequently suffer from exceptionally poor stability within complex biological fluids, where abundant endogenous proteolytic enzymes rapidly cleave peptide bonds and degrade the sequence, severely limiting their circulation half-life and functional bioactivity in vivo. This rapid enzymatic instability drastically curtails therapeutic efficacy and frequently necessitates frequent or excessively high dosing regimens to maintain therapeutic tissue concentrations. Advanced bioengineering approaches utilizing self-assembled peptide nanostructures, directional molecular assembly, and complete encapsulation within protective nanoparticles are being intensively explored to enhance stability and shield AMPs from aggressive host proteolysis [13, 171].

9.3 Short Half-Life and Rapid Degradation

Closely related to their proteolytic instability, low molecular weight AMPs exhibit short circulation half-lives due to rapid, non-specific degradation and high renal clearance rates. These small, low molecular weight peptides are quickly filtered out by the kidneys, necessitating the development of advanced drug delivery systems to prolong systemic retention times. Nanocarrier networks, such as N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers, have successfully demonstrated the ability to prolong circulation time by increasing the effective molecular weight of the peptide conjugate, thereby reducing renal filtration and enabling tumor-specific accumulation via the enhanced permeability and retention (EPR) effect [172].

9.4 Low Bioavailability

The vast majority of natural AMPs possess poor bioavailability, particularly when evaluated via oral administration pathways, due to rapid enzymatic digestion within the gastrointestinal tract and poor transport permeability through complex biological barriers. Consequently, the majority of clinically approved or investigational peptides strictly require parenteral routes of administration, which can compromise patient compliance and comfort. Modern innovations in formulation design, including injectable nanoparticles, specialized liposomes, and self-assembling biodegradable hydrogels, aim to improve baseline bioavailability and targeted delivery while minimizing unnecessary systemic exposure [170, 173].

9.5 Delivery Barriers in Solid Tumors

Delivering AMPs effectively into the dense core of solid tumors faces massive physiological obstacles, such as highly heterogeneous and dysfunctional tumor vasculature, elevated interstitial fluid pressure, dense extracellular matrix barriers, and the protective, immunosuppressive tumor microenvironment. These combined physical and biological barriers strictly limit deep peptide penetration, often reducing local drug concentrations below therapeutic thresholds. Sophisticated delivery systems that exploit specialized targeting ligands, stimuli-responsive release mechanisms, and multi-functional nanotechnology are currently under active investigation but require further optimization to achieve robust, uniform tumor penetration and long-term tissue retention [13, 174].

9.6 High Production Cost

The high cost of large-scale chemical synthesis and current manufacturing protocols remains a significant obstacle to commercial viability. Although recent advances in solid-phase chemical synthesis have successfully reduced base expenses, the sheer molecular complexity of highly modified, stapled, or conjugated AMP variants and the strict regulatory demand for exceptional purity substantially elevate production costs relative to traditional small-molecule drugs. Moreover, scalable, highly reproducible production methods for custom peptide nanoparticles and complex delivery formulations require extensive development before they can become commercially competitive and viable for widespread clinical adoption [173, 175].

9.7 Immunogenicity and Safety Concerns

Although AMPs generally exhibit a relatively low immunogenicity profile due to their endogenous host-defense nature, adverse immune responses and long-term safety concerns can still arise, especially when dealing with repeated systemic administration cycles or highly modified synthetic sequences. Advanced nanocarrier delivery systems and polymer conjugates can be utilized to mask and modulate this immunogenicity, but rigorous, high-throughput preclinical evaluation remains essential to fully map and minimize adverse immune reactions, neutralising antibody formation, and off-target inflammatory effects [13, 174].

9.8 Lack of Sufficient Clinical Evidence

Despite a massive and highly encouraging body of preclinical data, concrete clinical evidence supporting AMPs in oncology remains strictly limited, with few AMP-based anticancer therapies having successfully progressed beyond early-phase human trials. Efficacy challenges related to in vivo stability, targeted tumor delivery, off-target toxicity, and scalable manufacturing have historically slowed down broad clinical adoption. Consequently, more extensive, multi-center, and well-designed clinical studies are urgently required to definitively establish therapeutic efficacy, optimal dosing schedules, and long-term safety profiles across diverse human patient populations [13, 173].

10. Strategies to Improve Therapeutic Potential of Antimicrobial Peptides (AMPs) in Cancer Therapy

The therapeutic application of antimicrobial peptides as frontline anticancer agents faces strict bottlenecks, including proteolytic instability, limited bioavailability, rapid renal clearance, off-target cytotoxicity, and severe solid-tumor delivery barriers. To overcome these limitations and maximize overall clinical efficacy, a diverse array of advanced optimization and sequence-engineering strategies have been developed and are currently under active investigation.

10.1 Amino Acid Substitution and Sequence Modification

The rational modification of the primary amino acid sequence of AMPs through the systematic substitution of natural residues with non-natural, synthetic amino acids or altered charge-to-hydrophobicity profiles can vastly improve overall peptide stability, targeting selectivity, and membrane-disruptive interaction kinetics. This precision sequence engineering enhances baseline resistance against enzymatic degradation by proteases and can significantly increase structural affinity for cancer cell membranes by carefully optimizing the net positive charge and amphipathic alignment. Designing sequences based on strict structure-activity relationships (SAR) allows researchers to fine-tune anticancer lytic potency while maintaining toxicity to normal cells below hazardous thresholds [22, 24].

10.2 Cyclization and Peptide Stapling

Peptide cyclization via head-to-tail covalent linkage or the introduction of targeted internal disulfide bonds confers high conformational rigidity that stabilizes the bioactive three-dimensional structure of AMPs and drastically improves their resistance to exopeptidases. Similarly, hydrocarbon peptide stapling introduces rigid synthetic bridges across the peptide backbone to chemically stabilize alpha-helical or beta-sheet conformations, resulting in enhanced serum stability, superior cell permeability, and optimized receptor binding affinity. These structural conformational locks have successfully demonstrated increased circulation half-life and robust bioactivity in vivo [22].

10.3 D-Amino Acid Incorporation

Replacing standard, naturally occurring L-amino acids with their synthetic D-enantiomers effectively prevents proteolytic cleavage by endogenous host enzymes, as proteases fail to recognize the inverted chiral configuration, usually without compromising the peptide's primary lytic activity. D-amino acid-containing AMP architectures exhibit significantly prolonged serum half-lives and vastly increased metabolic stability in vivo, directly addressing one of the most historical and restrictive barriers to the clinical translation of peptide-based therapeutics [22].

10.4 PEGylation and Lipidation

The covalent attachment of functional polyethylene glycol (PEG) chains, known as PEGylation, increases the effective hydrodynamic size of the peptide conjugate, thereby reducing rapid renal clearance, shielding the AMP sequence from enzymatic proteases and host immune recognition, and significantly improving overall aqueous solubility. Concurrently, peptide lipidation via the conjugation of specific fatty acid chains enhances lipid membrane affinity, promotes rapid cellular uptake, and facilitates smooth insertion into the hydrophobic cores of tumor cell membranes. Both modifications work in tandem to improve systemic pharmacokinetics and tissue bioavailability while lowering the baseline immunogenicity of the payload [22].

10.5 Nanocarrier-Based Delivery

Nanoparticle-mediated delivery architectures protect fragile AMP payloads from enzymatic degradation, optimize target-site tumor homing, and enable precisely controlled cargo release kinetics. Platforms such as specialized liposomes, polymeric nanoparticles, inorganic nanomaterials, and self-assembling peptide nanostructures have been successfully deployed. Furthermore, engineering stimuli-responsive smart nanocarriers allows for the selective release of payloads only when exposed to specific tumor microenvironmental cues, such as an acidic local pH or hyper-expressed matrix metalloproteinase activity, enhancing specificity while facilitating multi-modal combination therapy and real-time cellular imaging [176, 177, 178].

10.6 Tumor-Targeted Peptide Engineering

The direct conjugation of AMPs to tumor-homing ligands or the strategic incorporation of precise receptor-targeting motifs increases selective binding and receptor-mediated uptake by cancer cells. Peptides engineered to be highly responsive to tumor-specific conditions, such as integrin-targeting RGD motifs, drastically improve tissue-level selectivity. Furthermore, engineering complex peptides for dual-receptor recognition can augment absolute solid-tumor penetration and tissue retention, driving therapeutic efficacy upward while minimizing systemic off-target toxicities [22, 176].

10.7 Combination with Chemotherapy, Radiotherapy, and Immunotherapy AMPs demonstrate exceptional therapeutic synergy when combined with established, conventional cancer treatments. Their primary membrane-disruptive actions physically permeabilize the tumor outer wall, sensitizing resistant cells to co-administered small-molecule chemotherapy and localized radiotherapy protocols. Additionally, their inherent immunomodulatory properties can be leveraged to augment anti-tumor adaptive immune responses. Advanced nanocarriers capable of co-delivering AMP sequences alongside conventional chemotherapeutic agents or novel immunostimulatory compounds enable powerful, multimodal combination therapies that systematically overcome complex multi-drug resistance mechanisms and reduce overall clinical dosing requirements [22, 177, 179].

10.8 AI-Based Design and Screening of Anticancer Peptides

The integration of artificial intelligence, high-throughput machine learning algorithms, and computational biology approaches is rapidly accelerating the discovery and optimization of novel, next-generation AMPs and anticancer peptides. These advanced computational tools can accurately predict peptide lytic activity, metabolic stability, and off-target toxicity profiles based solely on primary sequence data and simulated structural features. AI-driven nanocarrier optimization further enhances real-world pharmacokinetics and tumor targeting precision, streamlining preclinical screening pipelines and guiding personalized therapeutic design while reducing development time and costs [180, 181, 182].

11. Preclinical and Clinical Evidence of Antimicrobial Peptides (AMPs) in Cancer Therapy

The translational progression of antimicrobial peptides and advanced peptide-based therapeutics in clinical oncology encompasses a wide spectrum of contemporary research stages, moving rapidly from highly controlled in vitro cellular characterization to advanced, human clinical trials. Their evolving role reflects their clinical potential as precise, effective, and significantly safer next-generation oncologic agents.

11.1 In Vitro Studies Using Cancer Cell Lines

Extensive in vitro investigations have comprehensively characterized the primary anticancer properties of AMPs and custom peptide conjugates across diverse human cancer cell lines, demonstrating robust mechanical actions such as rapid membrane disruption, the direct induction of internal apoptotic pathways, and the targeted modulation of oncogenic intracellular signaling networks. These high-throughput studies have repeatedly validated the high selectivity of cationic sequences toward tumor surfaces, demonstrating minimal background toxicity to normal, healthy cells due to the distinct differences in outer membrane composition and surface charge density between malignant and healthy cells [24, 151]. In particular, cell-penetrating peptides (CPPs) have been instrumental in vitro for facilitating the highly efficient intracellular delivery of diverse therapeutic cargos—including small-molecule chemotherapeutics and fragile nucleic acids—vastly increasing cytotoxicity in resistant tumor models through verified receptor-mediated translocation pathways [183, 184].

11.2 In Vivo Animal Model Studies

Building upon this strong in vitro efficacy, in vivo animal model studies have successfully confirmed the therapeutic potential of AMPs by demonstrating significant tumor growth inhibition, the suppression of distant metastatic cascades, and drastically improved host survival rates. For example, dual-receptor-recognizing CPP-modified liposomal formulations loaded with paclitaxel extended overall survival in glioma-bearing mouse models by over twofold, showcasing exceptional tumor-homing precision and deep tissue penetration through challenging physiological barriers [154]. Concurrently, self-assembling peptide-based hydrogels and advanced peptide-drug conjugates (PDCs) evaluated in animal models have demonstrated superior in vivo stability, sustained local drug release profiles, and an elimination of systemic toxicity, contributing to enhanced therapeutic durability [159, 163]. Furthermore, multi-functional nanoparticle delivery systems that integrate potent innate immune agonists alongside tumor-specific targeting peptides have demonstrated the generation of robust antitumor adaptive immunity and extensive tumor burden reduction in highly aggressive, metastatic solid tumor models [131].

11.3 Peptides Currently Under Clinical Investigation

Human clinical trials investigating advanced peptide-based anticancer therapies are expanding globally, reflecting growing clinical confidence in their translational potential. Although no standalone cell-penetrating peptides (CPPs) or CPP-cargo complexes have yet received definitive FDA approval for cancer therapy, several highly promising candidates are currently undergoing early-phase human clinical evaluation, targeting specialized mechanisms such as improved local drug delivery, microenvironmental remodeling, and tumor-specific uptake [184]. Approved peptide therapeutics derived from natural sequences, peptide conjugates, and specialized analogues—including gonadotropin-releasing hormone (GnRH) analogues, somatostatin analogues, and prostate-specific membrane antigen (PSMA)-targeting peptides—have successfully paved the regulatory paths toward expanded clinical adoption. Moreover, the growing clinical success of peptide receptor radionuclide therapy (PRRT) and highly targeted antibody-drug conjugates (ADCs) incorporating structured peptide linkers highlights the ongoing translational momentum of this field [185, 186].

11.4 Approved Peptide-Based Anticancer Drugs and Their Relevance

Several peptide-based drugs have already obtained full FDA approval for direct cancer treatment or clinical management, providing clear evidence of the biochemical feasibility and high therapeutic value of peptide macromolecular therapeutics. Notably, gonadotropin-releasing hormone (GnRH) analogues are universally deployed as standard frontline agents in prostate and breast cancer management to drive targeted hormone suppression. In radiation oncology, peptide receptor radionuclide therapy (PRRT) agents, most notably lutetium-177 DOTATATE, have revolutionized the treatment of somatostatin receptor-positive neuroendocrine tumors by delivering highly localized cytotoxic radiation directly to the tumor site. Furthermore, advanced PSMA-targeting peptides and peptide-based ADCs exhibit exceptional specificity for prostate cancer cell lines, while classic somatostatin analogues remain widely applied in both neuroendocrine tumor diagnostics and active molecular therapy. These approved agents collectively exemplify the capacity of structured peptides to achieve high target specificity, acceptable patient safety profiles, and highly diverse therapeutic mechanisms, safely bridging the gap between molecular receptor targeting, cytotoxic payload delivery, and advanced diagnostic imaging [185, 187].

11.5 Gap Between Laboratory Findings and Clinical Translation

Despite exceptional and highly promising preclinical results, the widespread clinical translation of AMPs and peptide-based therapies faces strict barriers, including high proteolytic instability and a short in vivo half-life that severely limits systemic efficacy within human biological fluids. Solid-tumor delivery challenges, particularly regarding uniform penetration through dense extracellular matrices and overcoming the highly complex, immunosuppressive tumor microenvironment, present ongoing pharmacological hurdles. Furthermore, potential off-target toxicity and minor immunogenicity risks demand highly optimized, iterative peptide design and the development of biocompatible delivery vehicles. Finally, industrial scale-up bottlenecks, high manufacturing costs under Good Manufacturing Practice (GMP) conditions, and

complex regulatory validation paths heavily impact overall commercial viability. Ongoing international efforts address these limitations via chemical modifications, such as structural cyclization and D-amino acid incorporation, along with nanocarrier-based delivery platforms and multi-agent combination regimens, making rigorous, large-scale clinical trials critical to validate safety and efficacy across heterogeneous human patient populations [186, 188].

12. Future Perspectives in Antimicrobial Peptide-Based Cancer Therapy

The future landscape of antimicrobial peptide-based cancer therapy is rich with clinical potential, accelerated by recent technical advances and innovative, multidisciplinary approaches. Drawing from contemporary research, several key vectors outline the promising trajectories and translational milestones that will shape next-generation peptide therapeutics.

12.1 Personalized Peptide-Based Cancer Therapy

Personalized medicine is poised to completely revolutionize cancer treatment by tailoring therapeutic structures to match individual patient tumor profiles. Ongoing advances in computational peptide engineering have enabled the rapid development of bioactive peptides possessing high patient-specific tumor specificity, including customized peptide-drug conjugates (PDCs) optimized to match unique receptor expression patterns and personalized peptide vaccines designed from patient-specific tumor neoantigens. This high-level structural customization maximizes therapeutic efficacy while completely avoiding off-target side effects, positioning peptides as exceptionally powerful candidates for precision oncology applications [189].

12.2 Smart Delivery Platforms

Smart drug delivery systems are being engineered to systematically overcome the intrinsic biological limitations of wild-type AMPs, such as low metabolic stability and rapid proteolytic degradation. Supramolecular peptide-based hydrogels—with their highly tunable biological properties and customizable, controlled cargo release kinetics—dramatically enhance local peptide retention times and maintain high local bioactivity within the tumor site. Likewise, advanced polymeric nanocarriers engineered specifically for intracellular delivery facilitate reliable peptide access to vital intracellular targets, vastly improving therapeutic outcomes. Stimuli-responsive nanostructures that respond dynamically only to specific tumor microenvironment conditions, such as local hypoxia, acidic pH, or specific enzyme upregulations, promise selective, on-demand peptide release, effectively eliminating systemic toxicity [178, 190].

12.3 Immunotherapy-Peptide Combination Strategies

Peptides are occupying increasingly pivotal roles in modern cancer immunotherapy, acting as highly efficient tumor vaccines, immune checkpoint modulators, and molecular adjuvants. Combining membrane-active AMPs or specific anticancer peptides with advanced immunotherapies, such as chimeric antigen receptor (CAR)-T cell therapy or immune checkpoint inhibitors, significantly enhances local tumor immunogenicity and overall antitumor efficacy. Furthermore, peptide-based nanomaterials can function simultaneously as protective delivery scaffolds and active immune stimulators, facilitating the coordinated co-delivery of multiple therapeutic agents. These synergistic strategies aim to permanently dismantle local tumor resistance mechanisms and broaden therapeutic response rates across diverse patient populations [191, 192].

12.4 AI and Machine Learning in Peptide Discovery

Artificial intelligence (AI) and deep machine learning (ML) architectures are actively accelerating the discovery and structural optimization of novel, highly potent AMPs and anticancer peptides. These computational frameworks accurately predict real-world peptide lytic activity, serum stability, and target receptor interactions, enabling rational de novo design with unprecedented precision while drastically reducing the traditional experimental and screening burden. Additionally, AI-driven nanocarrier design significantly enhances pharmacokinetics and tumor-targeting precision, streamlining preclinical development pipelines and guiding personalized therapeutic strategies [180, 193].

12.5 Development of Safer and More Stable Peptide Analogues

Ongoing engineering efforts focus heavily on synthesizing peptide analogues characterized by enhanced protease resistance, minimized off-target toxicity, and optimized in vivo circulation half-lives. Chemical modifications such as fatty acid conjugation (lipidation), backbone cyclization, the strategic incorporation of D-amino acids, and advanced peptide backbone modifications protect the therapeutic sequences from rapid enzymatic proteolysis while maximizing favorable electrostatic interactions with cancer cell membranes, substantially raising the therapeutic index. Developing these optimized analogues is critical to successfully translating peptides from promising experimental agents into clinically viable, frontline drugs [22, 36].

12.6 Translational Pathway from Preclinical Research to Clinical Use

Successful clinical translation requires the systematic resolution of lingering stability, delivery, immunogenicity, and manufacturing scalability challenges. Standardizing large-scale chemical synthesis protocols, refining advanced nanoformulations, and implementing robust, standardized preclinical evaluation frameworks can streamline early-stage development pipelines. Furthermore, human clinical trial designs that incorporate specific molecular biomarkers and precise patient stratification will significantly enhance clinical evaluation metrics. As regulatory frameworks evolve to accommodate complex peptide-based and nanostructured therapeutics, the pathway toward formal regulatory approval will accelerate. Ultimately, the integration of multidisciplinary expertise spanning peptide chemistry, nanotechnology, molecular immunology, and clinical oncology remains the absolute key to realizing the full therapeutic potential of AMP-based cancer therapies [189, 190].

13. Conclusion

Antimicrobial peptides have successfully emerged as a highly promising, innovative class of next-generation anticancer therapeutic agents, exhibiting unique mechanical and biological features that clearly distinguish them from conventional oncology therapies. Their immense anticancer potential derives primarily from their charge-dependent selective targeting and subsequent mechanical disruption of cancer cell membranes, successfully exploiting the distinct differences in outer membrane lipid composition and negative surface charge that differentiate malignant cells from healthy tissue. Beyond asserting direct physical cytotoxicity, AMPs can initiate programmed apoptosis or acute necrosis through targeted mitochondrial dysfunction and massive reactive oxygen species generation, actively modulate local host immune responses to enhance long-term antitumor immunity, and directly interfere with vital tumor microenvironmental processes such as angiogenesis and metastatic signaling. These multifaceted, parallel actions contribute to their broad-spectrum efficacy across a wide variety of diverse cancer types, making them potent candidates for driving tumor regression and inhibiting metastasis. Among their principal clinical advantages, AMPs demonstrate highly preferential toxicity toward cancer cells while strictly sparing normal, zwitterionic host tissues, thereby minimizing the debilitating side effects typically associated with traditional chemotherapy.

Their exceptionally rapid mechanism of action and reliance on multi-targeted physical interactions result in a significantly lower likelihood of drug resistance development within changing tumor populations. Furthermore, the structural flexibility of the peptide backbone permits diverse chemical modifications—such as rational amino acid substitutions, cyclization, PEGylation, and lipidation—that optimize overall stability, selectivity, and pharmacokinetics. Combining these peptides with existing therapeutic modalities (chemotherapy, radiotherapy, immunotherapy) and incorporating them into novel delivery architectures like smart nanocarriers and supramolecular hydrogels further amplifies their clinical potential. However, widespread clinical translation remains challenged by intrinsic limitations, including poor stability and rapid degradation by proteases within biological fluids, short circulation half-lives, low

oral bioavailability, and severe delivery difficulties within dense solid tumors. Potential toxicity toward normal cells under high concentrations, immunogenicity risks upon repeated administration, and high industrial production costs present ongoing development barriers. Moreover, while preclinical evaluations continue to yield exceptional data, robust clinical evidence from human trials remains limited, emphasizing the urgent need for more extensive, multi-center studies to fully establish safety and efficacy profiles. Looking forward, the future integration of AMPs as mainstay cancer therapeutics hinges completely upon overcoming these challenges through innovative, cross-disciplinary strategies: executing precision structural optimization to maximize protease resistance, deploying smart delivery platforms for targeted and stimuli-responsive cargo release, designing personalized peptide sequences matched to individual tumor profiles, and leveraging AI-driven computational discovery to rapidly generate potent analogues. Ultimately, securing synergistic combinations with modern immunotherapies, alongside an advanced understanding of tumor microenvironment dynamics, will solidify their clinical impact.

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