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Antimicrobial Peptides in Human Health: Innate Immunity, Mechanisms of Action, Disease Associations and Clinical Translation. A Evidence-Based Medicine Narrative Review

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ABSTRACT

Antimicrobial peptides (AMPs) are evolutionarily ancient, structurally diverse molecules that form a critical first line of innate immune defense across all domains of life. In humans, AMPs include the α- and β-defensin families, the cathelicidin LL-37, histatins, dermcidin, granulysin, and numerous other endogenous host defense peptides, collectively constituting a sophisticated multimodal system capable of direct microbicidal activity, immunomodulation, and barrier maintenance. This evidence-based narrative review addresses four interconnected dimensions of AMP biology relevant to the clinician and researcher. First, the structural classification of human AMPs, their cellular sources, and mechanisms of action are reviewed, encompassing membrane-disruptive models (barrel-stave, toroidal pore, carpet), cell wall synthesis inhibition (lipid II targeting), intracellular targeting, and immunomodulatory mechanisms. Second, the expanding roles of AMPs beyond direct killing are discussed — including chemotaxis, toll-like receptor (TLR) modulation, wound healing, angiogenesis, and the bridging of innate and adaptive immunity. Third, the bidirectional relationships between AMP dysregulation and human disease are examined across eight clinical conditions: atopic dermatitis, psoriasis, Crohn's disease, sepsis, COVID-19 and respiratory infections, systemic lupus erythematosus, rosacea, and cancer. Fourth, the clinical translation pipeline is reviewed for ten AMPs currently approved, in late-stage trials, or recently completing Phase II/III development — including polymyxin B/colistin, daptomycin, rezafungin (FDA-approved 2023), omiganan, pexiganan, brilacidin, LL-37, NP213 (novexatin), murepavadin, and DPK-060. The current challenges to clinical translation — protease susceptibility, cytotoxicity, bioavailability, manufacturing cost — and the emerging solutions including D-amino acid substitution, peptide-mimetics, nanoparticle encapsulation, and AI-driven AMP discovery are also reviewed. The global burden of antimicrobial resistance (AMR), responsible for an estimated 4.9 million attributable deaths in 2019, makes the clinical development of AMP-based therapeutics a scientific and public health imperative.

Keywords

Antimicrobial peptides, Host defense peptides, Defensins, Cathelicidins, LL-37, hBD-2, Innate immunity, Antimicrobial resistance, Membrane disruption, Immunomodulation, Antibiofilm, Clinical trials, Pexiganan, Omiganan, Daptomycin, Rezafungin, Brilacidin, Atopic dermatitis, Psoriasis, Crohn's disease, Sepsis, AI-assisted drug discovery.

Introduction

The recognition that multicellular organisms require a rapid, pre-formed first line of defense against microbial invasion — one that operates before the slower, antigen-specific adaptive immune response can be mobilized — predates modern immunology [1]. In 1956, phagocytin was isolated from rabbit leucocytes as the first described animal antimicrobial peptides (AMP); in 1981, cecropins were characterized from silkworm moths; and Michael Zasloff's 1987 discovery of magainins from Xenopus frog skin catalyzed the modern era of AMP research. Today, the APD3 (Antimicrobial Peptide Database) catalogues over 3,300 natural AMPs, 231 predicted sequences, and 1,299 synthetic variants — a landscape reflecting decades of research across all living kingdoms. AMPs are now understood not merely as endogenous

antibiotics but as multifunctional immunomodulatory molecules that integrate diverse effector and regulatory functions of innate immunity [2-4] (Figure 1).

The clinical urgency for AMP research is rooted in the global antimicrobial resistance (AMR) crisis. Murray et al. estimated 4.9 million deaths attributable to bacterial AMR in 2019, with six pathogens — *E. coli*, *S. aureus*, *K. pneumoniae*, *S. pneumoniae*, *A. baumannii*, and *P. aeruginosa* — responsible for the majority [1]. The conventional antibiotic pipeline has progressively narrowed, with fewer than ten genuinely novel antibiotic classes introduced since 1960. AMPs offer a mechanistically distinct alternative: their primary mechanism of action — disruption of the microbial membrane — is structurally encoded in their own amphipathic architecture rather than dependent on a discrete molecular target susceptible to point mutation, making resistance development substantially slower and more difficult [2,3]. Additionally, their immunomodulatory properties — modulating host inflammatory responses rather than acting exclusively as direct microbicides — offer a host-directed therapeutic dimension absent from conventional antibiotics [5].

At the same time, AMP dysregulation underlies or contributes to a remarkable breadth of human pathology beyond infection: inflammatory dermatological conditions (atopic dermatitis, psoriasis, rosacea), autoimmune diseases (systemic lupus erythematosus [SLE], inflammatory bowel disease [IBD; e.g., Crohn's disease]), respiratory conditions (asthma, COPD exacerbations, COVID-19 severity), and even cancer biology [6-11]. Understanding the conditions under which AMPs are induced, suppressed, or aberrantly expressed is therefore clinically consequential far beyond infectious disease.

This short review provides a comprehensive, clinically oriented synthesis of human AMP biology, disease associations, and therapeutic development, aimed at the clinician and clinical researcher seeking to integrate this rapidly evolving field into practice and research.

Methods

A systematic search was conducted across PubMed/MEDLINE (2000 to February 2026), Cochrane Library, Embase (1974 to February 2026), and Web of Science (2000 to February 2026). Primary MeSH terms: ("Antimicrobial Peptides"[MeSH] OR "Defensins"[MeSH] OR "Cathelicidins"[MeSH]) AND ("Immunity, Innate"[MeSH] OR "Anti-Infective Agents"[MeSH]

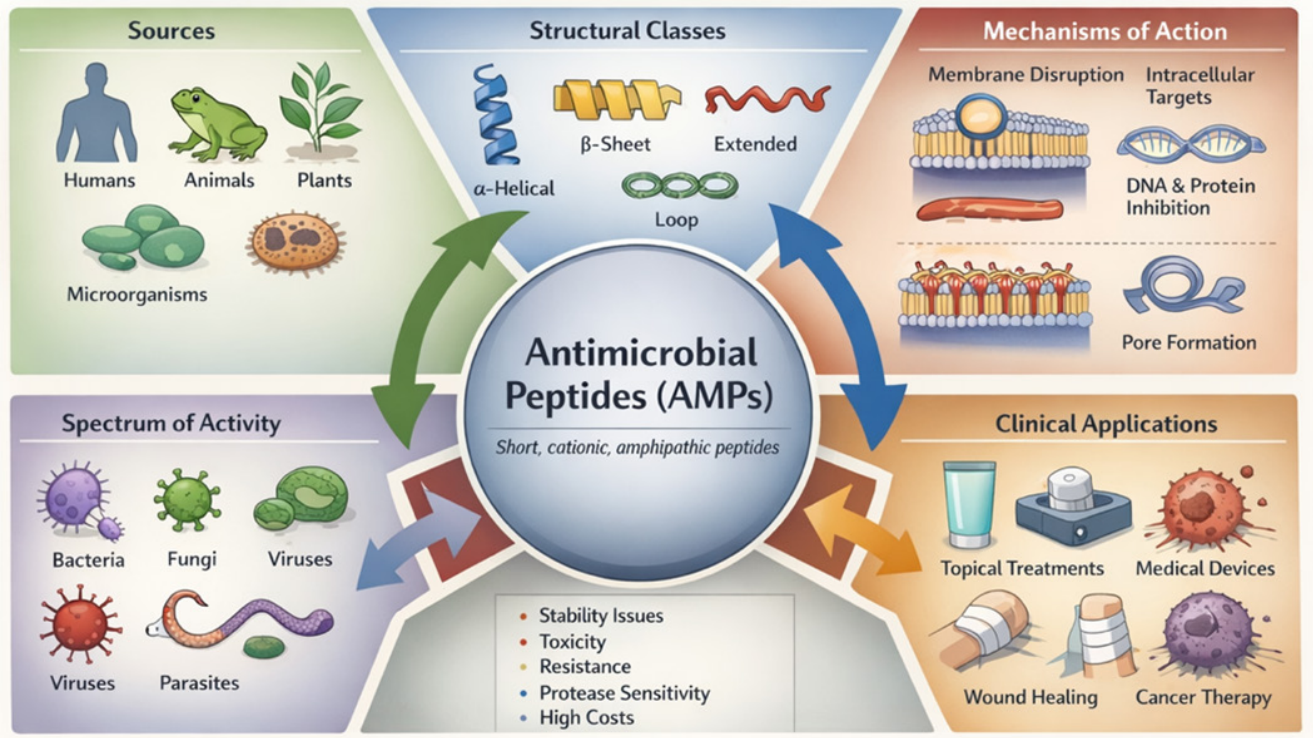

Figure 1: Overview of Antimicrobial Peptides (AMPs): Sources, Structural Classes, Mechanisms of Action, and Clinical Applications.

Legend: Schematic representation of antimicrobial peptides (AMPs) highlighting their biological origins, structural diversity, mechanisms of action, and therapeutic applications. AMPs are evolutionarily conserved, short, cationic, amphipathic peptides produced by organisms across multiple kingdoms, including animals, plants, and microorganisms. Structurally, AMPs are classified into four principal conformational groups: α-helical, β-sheet, extended, and loop peptides. Their primary mechanisms of antimicrobial activity involve disruption of microbial membranes through pore formation or membrane destabilization, as well as intracellular targeting, including inhibition of nucleic acid and protein synthesis. AMPs exhibit broad-spectrum activity against bacteria, fungi, viruses, and parasites. Clinically, they are being developed or used in topical treatments, wound healing, and management of multidrug-resistant infections. Key translational challenges include protease susceptibility, potential toxicity, stability limitations, resistance development, and high production costs.

OR "Drug Resistance, Bacterial" [MeSH]). Free-text supplementary terms included names of specific AMPs and conditions. ClinicalTrials.gov was searched for registered AMP trials. Reference lists of all included systematic reviews and major guidelines were hand-searched. Searches for AI-based AMP discovery were supplemented with machine learning and deep learning terms [12-14].

Studies were included if they fulfilled: (1) study design: RCTs, prospective or retrospective cohort studies (n ≥ 30), in vitro mechanistic studies using human cells or human AMPs, diagnostic accuracy studies, systematic reviews with meta-analyses, and evidence-based clinical guidelines; (2) population: human subjects, human-derived cells or tissues, human AMP sequences; and (3) outcomes: AMP expression, antimicrobial activity (MIC, MBC), immunomodulatory functions, disease association data, clinical trial endpoints, pharmacokinetic data.

Classification and Structural Properties of Human AMPs

Human AMPs are a structurally diverse group of molecules unified by common functional properties: they are typically cationic (carrying a net positive charge at physiological pH), amphipathic (possessing distinct hydrophilic and hydrophobic domains), and small (ranging from 7 to ~100 amino acids, with most falling between 12 and 50 residues) [4,15]. These structural features — particularly the combination of positive charge and amphipathicity — underlie their preferential interaction with the negatively charged bacterial membrane surface (enriched in phosphatidylglycerol, cardiolipin, and lipopolysaccharide) relative to the net-neutral mammalian cell membrane (dominated by phosphatidylcholine and sphingomyelin in the outer leaflet) [2,16]. Table 1 summarizes the principal classes of human AMPs, their structural features, cellular sources, and key functions [4,15,17].

Alpha-defensins: the neutrophil and Paneth cell sentinels

Alpha-defensins are the most extensively characterized human AMPs [4,17,18]. The four neutrophil-derived forms (HNP-1 through HNP-4) are stored preformed in azurophil granules and released upon phagocytic activation; their concentrations within the phagolysosome can reach tens of milligrams per milliliter, conferring direct microbicidal activity via membrane disruption. HD-5 and HD-6, expressed by Paneth cells in the intestinal crypts of the small intestine, serve a fundamentally different architectural function: they are secreted into the intestinal lumen where they establish antimicrobial gradients protecting the epithelium from luminal pathogens and regulating intestinal microbiome composition [4,15,17]. HD-6 uniquely forms nanoscale fibers that physically trap pathogens at the mucosal surface. The importance of this system is demonstrated by the association between NOD2 loss-of-function mutations (present in 15–25% of Crohn's disease patients) and impaired HD-5/HD-6 secretion [19,20] — a key pathophysiological link discussed in the disease association section.

Beta-defensins: the epithelial sentinels

Human beta-defensins (hBD-1 through hBD-4, and beyond) are the principal AMPs of epithelial surfaces — skin, lung, gastrointestinal tract, and genitourinary mucosa [4,15,17]. hBD-1 is constitutively expressed but requires reduction by the GILT enzyme (lysosomal thiol reductase) for full antimicrobial activity. hBD-2 and hBD-3

Table 1: Classification of principal human antimicrobial peptides: structure, cellular source, and key functions [4,15,17].

Class	Representative human AMPs	Structure	Size (aa)	Primary source / expression	Key function
α-Defensins	HNP-1–4; HD-5, HD-6	β-sheet, 3 disulfide bonds	29–35	HNP-1–4: neutrophil granules; HD-5/6: Paneth cells (small intestine)	Direct microbicidal; intestinal barrier; NF-κB activation
β-Defensins	hBD-1, hBD-2, hBD-3, hBD-4	β-sheet, 3 disulfide bonds (less constrained)	36–42	Epithelial cells: skin, lung, GI, urogenital; inducible (hBD-2/3) or constitutive (hBD-1)	Broad-spectrum antimicrobial; CCR6-mediated chemotaxis of DCs and memory T cells; wound healing
Cathelicidins	LL-37 (hCAP-18 C-terminus)	α-helix (amphipathic)	37	Neutrophils, monocytes, NK cells; skin, lung, gut epithelium; vitamin D3-inducible	Membrane disruption; chemotaxis (FPRL1); immunomodulation; wound healing; angiogenesis
Histatins	Histatin-1, -3, -5	Linear, histidine-rich	7–38	Salivary glands (parotid, submandibular); constitutive secretion	Antifungal (Candida, Cryptococcus); salivary innate defence; wound healing
Dermcidin (DCD)	DCD-1L, SSL-25	Anionic α-helical	47	Sweat gland eccrine secretion; constitutive; regulated by thermal/osmotic stress	Unique anionic mechanism; active at low pH; forms zinc-gated ion channels; skin microbiome control
Granulysin	Granulysin (15 kDa; 9 kDa)	SAPOSIN-fold	74 (15 kDa)	Cytotoxic T lymphocytes; NK cells; secretory lysosomes	Mycobacterial/fungal killing; apoptosis induction; synergistic with perforin/granzyme
Theta (θ)-defensins	No functional human gene (pseudogene DEFT1P)	Cyclic, macrolactam ring	18	Non-human primates; human gene silenced by premature stop codon; retrocyclin-1 retrocyclins synthesised artificially	HIV entry inhibition; potential therapeutic candidate (retrocyclins)

AA = Amino acids; CCR6 = CC chemokine receptor 6; DCs = Dendritic cells; EPS = Extracellular polymeric substance; FPRL1 = Formyl peptide receptor-like 1; GI = Gastrointestinal; HNP = Human neutrophil peptide; MDR = Multidrug-resistant; NK = Natural killer; NF-κB = Nuclear factor kappa B.

are strongly inducible by pro-inflammatory stimuli (IL-1β, TNF-α, LPS, microbial components) via NF-κB and AP-1 pathways. Critically, their expression is suppressed by Th2 cytokines (IL-4, IL-13) — mechanistically explaining the profound susceptibility of atopic dermatitis lesional skin to *S. aureus* superinfection [7,8,21]. Beyond direct killing, hBD-2 and hBD-3 serve as chemokines: hBD-2 binds CCR6 on immature dendritic cells and memory T cells; hBD-3 also activates TLR1/2 dimers on macrophages, inducing pro-inflammatory cytokine secretion and phagocyte activation. These chemokine-like properties make beta-defensins molecular bridges between innate and adaptive immunity [5].

LL-37: the human cathelicidin

LL-37, derived from the 18-kDa precursor hCAP-18 by proteolytic cleavage, is the sole human cathelicidin and arguably the most multifunctional AMP characterized to date [15,22,23]. Its expression is regulated by multiple pathways including vitamin D3 (via a vitamin D response element, VDRE, in the CAMP gene promoter), hypoxia (HIF-1α), butyrate (produced by commensal bacteria — a microbiome-immunity interface), and inflammatory stimuli (NF-κB) [11,23,24]. LL-37 adopts an amphipathic α-helical structure in membrane-associated environments, enabling both membrane disruption and receptor-mediated immunomodulation [2,16]. Key immunological activities include: chemotaxis of

Table 2: Mechanisms of action of antimicrobial peptides: molecular description and clinical relevance [5,16,26].

Mechanism	Target	Molecular description	Clinical / therapeutic relevance
Barrel-stave pore	Bacterial membrane (anionic phospholipids)	Peptides insert perpendicularly into the bilayer; assemble into transmembrane pores with hydrophobic residues facing the lipid core and hydrophilic residues lining the channel. Water-filled pore → ion leakage → depolarisation → cell death.	Relevant for magainins, alamethicin, amphotericin B. Provides physical, sequence-independent channel with minimal protein target mutations possible.
Toroidal pore	Bacterial & eukaryotic membranes	Peptide-lipid cooperative structure: peptides insert and cause membrane to curve inward, forming a pore lined by both peptide and lipid head groups. Less stable than barrel-stave; more disruptive per peptide molecule.	Relevant for LL-37, magainin-2, melittin. LL-37 toroidal pore formation underpins rapid killing of Gram-positive and Gram-negative bacteria including MDR strains.
Carpet model	Membrane outer leaflet	Peptides accumulate parallel to membrane surface, forming a 'carpet' that causes detergent-like solubilisation (micellisation) of the lipid bilayer at threshold concentration. Does not require insertion into bilayer.	Cathelicidins, dermaseptins, cecropins. Effective at higher concentrations; relevant for biofilm disruption and surface colonisation prevention.
Cell wall synthesis inhibition	Lipid II (peptidoglycan precursor)	AMPs bind lipid II — the essential carrier for peptidoglycan building blocks. Sequestration prevents transglycosylation and transpeptidation steps. Most lantibiotic AMPs (nisin, mersacidin) operate via this mechanism.	Nisin (food-approved; oral cancer trials NCT06097468). Plectasin targets lipid II via calcium-dependent supramolecular mechanism (*Jekhmane, Nat Microbiol, 2024*). Very low resistance generation versus conventional cell-wall antibiotics.
Intracellular targets	DNA, RNA, ribosomes, metabolic enzymes, chaperones	Translocation across intact membrane (proline-rich AMPs, buforin II, PR-39); binding to nucleic acids → inhibition of transcription/translation; interference with protein folding. Multi-target action significantly reduces resistance probability.	Proline-rich AMPs (Bac5, Bac7) enter E. coli via SbmA transporter; fail to accumulate in resistant strains lacking SbmA. Highly selective for prokaryote ribosomes (70S vs 80S). Template for peptide antibiotics targeting Gram-negative pathogens.
Immunomodulation	Host immune receptors: FPRL1, CCR6, TLR2, TLR4, EGFR, P2X7	Indirect antimicrobial effect via: (1) chemotaxis of neutrophils, monocytes, DCs, NK cells; (2) modulation of TLR4 signalling (LPS neutralisation); (3) induction of cytokine/chemokine expression; (4) promotion of DC maturation and T-cell polarisation; (5) inhibition of neutrophil apoptosis.	LL-37 via FPRL1: chemoattraction of phagocytes to infection site. hBD-2/3 via CCR6: DC/T-cell recruitment bridging innate and adaptive immunity. IDR (innate defence regulator) peptides derived from LL-37 — clinical development for inflammatory/ infectious diseases. Anti-LPS activity of LL-37 relevant in sepsis models.
Antibiofilm activity	Extracellular matrix; quorum sensing; surface adhesion	Disruption of EPS (extracellular polymeric substance) matrix integrity; inhibition of initial adhesion and surface colonization; interference with quorum sensing signals; enhanced penetration of conventional antibiotics into biofilm.	LL-37 prevents biofilm formation by MRSA, P. aeruginosa, A. baumannii, S. epidermidis, E. coli at sub-MIC concentrations. Critical for medical device-related infections (65% of all infections involve biofilm). Synergistic use with antibiotics reduces MIC 4–16 fold.

AMP = Antimicrobial peptide; CCR6 = CC chemokine receptor 6; DC = Dendritic cell; EGFR = Epidermal growth factor receptor; EPS = Extracellular polymeric substance; FPRL1 = Formyl peptide receptor-like 1; IDR = Innate defense regulator; LPS = Lipopolysaccharide; MDR = Multidrug-resistant; MIC = Minimum inhibitory concentration; MRSA = Methicillin-resistant S. aureus; NK = Natural killer; TLR = Toll-like receptor

neutrophils, monocytes, and T cells via FPRL1 [22]; induction of IL-8/CXCL8 production (neutrophil chemokine); modulation of TLR4 signaling (acting as both LPS neutralizer and TLR4 agonist, context-dependent); inhibition of neutrophil apoptosis via P2X7/PI3K/Mcl-1 pathway (extending innate cell lifespan at infection sites); promotion of wound healing and angiogenesis (via VEGF induction and EGFR activation) [25]; and — in the context of psoriasis and SLE — formation of self-DNA/RNA complexes that activate innate immune sensing pathways [6,9].

Mechanisms of Action: From Membrane Disruption to Immunomodulation

The mechanisms by which AMPs exert their biological effects encompass a spectrum from direct physical membrane disruption to sophisticated immunological regulation of host cellular responses. Table 2 provides a comprehensive overview of the principal mechanisms with their molecular basis and clinical/therapeutic implications [2,3,16].

Selectivity for bacterial over mammalian membranes: the electrostatic hypothesis

The selective toxicity of AMPs for bacterial membranes over mammalian cells — the fundamental prerequisite for therapeutic use — rests on compositional differences between prokaryotic and eukaryotic cell surfaces. Bacterial membranes are enriched in anionic phospholipids (phosphatidylglycerol, cardiolipin) in the outer leaflet, and Gram-negative bacteria additionally present lipopolysaccharide (LPS) with its highly anionic lipid A and core polysaccharide. Mammalian outer membrane leaflets, by contrast, are dominated by zwitterionic phosphatidylcholine, sphingomyelin, and glycolipids, with anionic phosphatidylserine and phosphatidylinositol predominantly in the inner leaflet [2,3,16]. Cationic AMPs therefore preferentially accumulate on bacterial surfaces via electrostatic attraction at concentrations insufficient to disrupt mammalian membranes. The presence of cholesterol in mammalian but not bacterial membranes also stabilizes eukaryotic bilayers against AMP-induced disruption [2,16]. This selectivity is not absolute — cytotoxicity at supra-therapeutic concentrations is a persistent challenge for translational development — but provides a sufficient therapeutic window for topical and some systemic applications.

Resistance to AMPs: mechanisms and clinical implications

Although AMP resistance is substantially less frequent and slower to develop than conventional antibiotic resistance (a consequence of the non-specific membrane target), it is not absent and constitutes a clinically relevant concern for therapeutic development [2,3,27]. Known bacterial resistance mechanisms include: (1) modification of surface charge — D-alanylation of teichoic acids (*S. aureus* dltA/dltB genes) or lysylation of phosphatidylglycerol (MprF gene) reduces anionic surface charge, reducing AMP electrostatic attraction; (2) AMP-degrading proteases — *S. aureus* produces aureolysin and other proteases that cleave LL-37; Group A Streptococcus M1 protein sequesters cathelicidin; (3) efflux pumps — the MtrCDE efflux system in N. gonorrhoeae and related systems in Gram-negatives export AMPs; (4) outer membrane modifications — LPS modifications (mcr genes for colistin resistance) in Gram-negative bacteria reduce LPS anionic charge; (5) biofilm formation — EPS matrix adsorbs AMPs before they reach the bacterial membrane [27-30]. Strategies to counter AMP resistance include D-amino acid substitution (resistant to bacterial proteases), cyclisation (structural stability), and combination with conventional antibiotics (synergistic anti-biofilm activity) [27,31].

Antimicrobial Peptides in Human Disease: Dysregulation and Pathophysiology

Beyond their role in infection defense, human AMPs participate in, contribute to, or are dysregulated in a wide range of non-infectious diseases. Table 3 provides a detailed disease-specific summary [6,9,10,19].

Skin barrier diseases: the atopic dermatitis–psoriasis dichotomy

Atopic dermatitis (AD) and psoriasis represent opposing extremes of AMP expression in inflammatory skin disease, with contrasting clinical consequences. In AD, the Th2-dominated immune environment — characterized by IL-4, IL-13, and IL-31 overproduction — directly suppresses transcription of both CAMP (encoding hCAP-18/LL-37) and DEFB4A (encoding hBD-2) in keratinocytes [7,8,11]. The practical result is a striking paucity of antimicrobial peptides in AD lesional skin despite intense inflammation — explaining the paradoxical predisposition of AD patients to recurrent *S. aureus* superinfection (affecting > 90% of AD skin), eczema herpeticum (disseminated HSV infection), and other cutaneous infections not seen at equivalent rates in psoriatic skin [7,8,21]. In contrast, psoriatic skin overexpresses LL-37, hBD-2, and hBD-3 at 10–1000-fold normal levels — conferring significant resistance to cutaneous infection — but paying a pathological price: excess LL-37 complexes with self-DNA/RNA to bypass innate immune tolerance, activating plasmacytoid dendritic cell TLR7/9 and triggering the type I interferon cascade that initiates and sustains the psoriatic inflammatory loop [6,11]. This 'AMP paradox' has profound therapeutic implications: treatments targeting the Th2 axis in AD (dupilumab — anti-IL-4Rα) partially restore hBD-2 and LL-37 expression, reducing infection episodes; treatments targeting the Th17 axis in psoriasis could theoretically reduce AMP-mediated auto-activation.

Paneth cell defensins and Crohn's disease

The discovery that Paneth cell α-defensins (HD-5 and HD-6) constitute the principal small intestinal antimicrobial barrier, and that their secretion is impaired in ileal Crohn's disease, represents one of the most mechanistically consequential AMP-disease associations identified to date [19,20]. HD-5 and HD-6 are secreted constitutively and in response to bacterial stimulation into the intestinal crypts, where they establish an antimicrobial concentration gradient protecting the stem cell niche. HD-5 directly kills Salmonella, *E. coli*, and Listeria; HD-6 forms physical nanoscale fibers that trap pathogens. NOD2 (CARD15) loss-of-function variants — present in 15–25% of Crohn's patients — impair Paneth cell secretory responses, reducing HD-5 and HD-6 secretion by 50–80% in ileal Crohn's [19,20]. The resulting

Table 3: Antimicrobial peptides in human disease: expression changes, pathophysiological roles and clinical implications [6,9,19].

Disease / Context	AMP involved	Expression change	Pathophysiological role and clinical implication
Atopic dermatitis (AD)	hBD-2, hBD-3, LL-37	MARKEDLY REDUCED vs psoriasis and healthy skin	Th2-dominated inflammation (IL-4, IL-13, IL-31) suppresses DEFB4A/CAMP gene expression → deficient barrier AMP expression. Explains paradoxical susceptibility to S. aureus, HSV (eczema herpeticum) in AD despite skin inflammation. Th2 cytokines (IL-4/IL-13) directly suppress CAMP and DEFB4 transcription. Therapeutic rationale: vitamin D supplementation, dupilumab (anti-IL-4Rα) paradoxically restores some AMP expression.
Psoriasis	LL-37, hBD-2, hBD-3	MARKEDLY ELEVATED (10–1000× vs healthy skin)	Excess LL-37 complexes with self-DNA/RNA → activates plasmacytoid dendritic cell TLR7/TLR9 → type I interferon storm → Th17/IL-23 cascade. LL-37-DNA complexes circumvent nuclease degradation. Anti-LL-37 antibodies detectable in psoriasis serum (autoimmune dimension). Gallo RL et al., Nat Immunol 2007: established LL-37 as initiator of psoriatic inflammation. Paradoxically, elevated AMPs protect psoriatic skin from bacterial superinfection.
Inflammatory bowel disease (IBD): Crohn's disease	HD-5, HD-6 (Paneth cell α-defensins); hBD-1	HD-5/6 REDUCED in ileal Crohn's; hBD-1 constitutively low	NOD2 mutations (15–25% Crohn's) impair Paneth cell AMP secretion (HD-5/6) → deficient ileal antimicrobial net → dysbiosis, mucosal invasion by adherent-invasive E. coli (AIEC). HD-5/HD-6 also form lectins binding microvillous carbohydrates to trap pathogens. hBD-1 requires GILT reductase activation — impaired in Crohn's. Restoring Paneth cell function (HD-5/6 supplementation) represents therapeutic strategy.
Sepsis	LL-37; HNP-1–3; hBD-1/2; lactoferrin	INITIALLY elevated; then DEPLETED with clinical deterioration	Paradox: high initial AMPs activate TLR4/FPRL1 → cytokine storm contribution; chronic sepsis depletes AMP reserves → secondary infection susceptibility. Plasma LL-37 levels correlate inversely with sepsis severity and mortality. Administration of synthetic IDR-1 (innate defense regulator derived from LL-37) reduced lethal sepsis in mouse models without direct antimicrobial effect — pure immunomodulatory mechanism.
Respiratory infections (COVID-19; pneumonia)	LL-37; hBD-2; hBD-3	REDUCED in severe COVID-19; LL-37 inversely correlates with severity	Vitamin D3 deficiency (common in COVID-19 severity) → reduced LL-37 expression (vitamin D response element in CAMP gene) → impaired innate mucosal defense. LL-37 directly inhibits SARS-CoV-2 entry via ACE2 interference and inhibits viral replication. Epidemiological correlation: populations with lower vitamin D status (melanised skin, elderly, institutionalised) have lower baseline LL-37 and higher COVID-19 severity. Di YP et al., Physiol Rev 2024: comprehensive lung AMP review.
Lupus erythematosus (SLE)	LL-37; HNP-1–3	ELEVATED; LL-37-DNA complexes in circulation	Self-DNA released from neutrophil extracellular traps (NETs) forms complexes with LL-37 → activates pDC TLR7/9 → type I interferon signature (hallmark of SLE). LL-37 shields DNA from DNase I degradation. NET-derived LL-37-DNA complexes are the primary trigger of the interferon signature in > 70% of SLE patients (Lande R et al., Nat Med 2011). Anti-LL-37 auto-antibodies detected in SLE patients.
Rosacea	LL-37 (CAMP); cathelicidin	ELEVATED; abnormal processing by kallikrein 5 (KLK5)	KLK5 (serine protease) abnormally elevated in rosacea skin → excessive cleavage of hCAP-18 → accumulation of short LL-37 peptides with enhanced pro-inflammatory but reduced direct antimicrobial activity → vasodilation (angiogenic effect via VEGF), neutrophil infiltration, TLR2-mediated inflammation. Vitamin D3 and kallikrein-5 inhibitors reduce LL-37 abnormal processing. Gallo RL lab (UCSD): established this mechanism 2007.
Cancer (diverse)	LL-37; hBD-1/2/3; HNP-1–3	COMPLEX: tumor-suppressive or tumor-promoting depending on cancer type	Tumour-suppressive: HNP-1 induces apoptosis in T-cell leukaemia, Burkitt lymphoma; hBD-1 (DEFB1) functions as tumour suppressor in renal/bladder carcinoma (promoter methylation silences DEFB1). LL-37: induces apoptosis in lung/colon cancer; inhibits tumorigenesis in colon cancer models. Tumour-promoting: LL-37 promotes angiogenesis and invasiveness in some contexts (ovarian, prostate, breast cancer). Clinical exploitation: LL-37 intra-tumoral injection melanoma Phase I/II 2024.

AD = Atopic dermatitis; AIEC = Adherent-invasive *E. coli*; CCR6 = CC chemokine receptor 6; DEFB1 = Defensin beta-1 gene; EPS = Extracellular polymeric substance; ERM = Extracellular polymeric substance; FPRL1 = Formyl peptide receptor-like 1; GILT = Gamma-interferon-inducible lysosomal thiol reductase; hBD = human beta-defensin; HD = Human defensin; HNP = Human neutrophil peptide; IBD = Inflammatory bowel disease; IL = Interleukin; KLK5 = Kallikrein-5; LPS = Lipopolysaccharide; MDR = Multidrug-resistant; NET = Neutrophil extracellular trap; NK = Natural killer cell; NOD2 = Nucleotide-binding oligomerisation domain 2; pDC = Plasmacytoid dendritic cell; SLE = Systemic lupus erythematosus; TLR = Toll-like receptor; VEGF = Vascular endothelial growth factor.

deficiency in antimicrobial gradient leads to microbiome dysbiosis, impaired clearance of adherent-invasive *E. coli* (AIEC), and mucosal invasion. This mechanism provides a pathophysiological explanation for why NOD2 mutations specifically predispose to ileal (rather than colonic) Crohn's — the anatomical site where Paneth cell AMPs are most important. Strategies to restore Paneth cell AMP secretion represent a rational therapeutic approach [20].

LL-37 in autoimmunity: the neutrophil extracellular trap connection

Neutrophil extracellular traps (NETs) — web-like structures of DNA, histones, and granule proteins including LL-37 released by activated/dying neutrophils — have emerged as a central pathophysiological mechanism in SLE and a growing list of autoimmune conditions [9]. Self-DNA within NETs forms tightly associated complexes with LL-37, which serves two pathological functions: (1) it protects NET-derived DNA from nuclease (DNase I) degradation in plasma, dramatically extending its immune-stimulatory half-life; (2) the LL-37-DNA complex is internalized by plasmacytoid dendritic cells (pDCs) via FcγRIIa (CD32a), where it activates TLR7 (for RNA complexes) or TLR9 (for DNA complexes), triggering type I interferon (IFN-α/β) production [9]. This self-sustaining IFN-α/β loop is the hallmark molecular signature of SLE, present in > 70% of patients. Lande et al. established LL-37-NET complexes as the dominant TLR9 activator in SLE pDCs [9]. Autoantibodies against LL-37 are detectable in the circulation of SLE patients, identifying LL-37 itself as an autoantigen. Targeting LL-37-NETs, DNase I activity enhancement or NET formation (PAD4 inhibitors) represent rational therapeutic strategies currently in early development.

Clinical Translation: The AMP Therapeutic Pipeline

The development of AMPs as clinical therapeutics has faced persistent challenges despite the mechanistic rationale for their use [32]. Of the thousands of natural and synthetic AMPs characterized in vitro, fewer than 50 have entered clinical trials, and approval has been achieved for a small subset [30,33]. The most common barriers to translation include protease susceptibility (leading to short plasma half-life), salt sensitivity (loss of antimicrobial activity at physiological ionic strength), cytotoxicity at concentrations required for systemic use, and manufacturing cost. However, a growing number of AMPs have reached Phase II and Phase III trials, and several important approvals have been achieved. Table 4 summarizes the current landscape of clinically advanced AMPs [27,30,33,34].

Overcoming Translation Barriers: Peptide Engineering and AI-Assisted Discovery

Chemical and structural optimization strategies

The major translational barriers facing natural AMPs — protease susceptibility, salt sensitivity, cytotoxicity, and manufacturing cost — have driven the development of systematic peptide engineering strategies. D-amino acid substitution replaces L-residues with their stereoisomers, rendering the peptide resistant to L-specific proteases (serine, cysteine, metallo-proteinases) while preserving the amphipathic architecture required for membrane disruption [27,31]. Cyclisation — achieved through disulfide bonds, macrolactam rings (as in NP213/novexatin), or side-chain linkages — confers structural rigidity and protease resistance while maintaining activity. Peptidomimetics — non-peptide molecules that mimic AMP structure and function — represent the extreme of this spectrum: brilacidin is an arylamide defensin-mimetic that retains broad-spectrum activity with reduced protease vulnerability. Truncation and minimal pharmacophore identification have yielded shorter, more tractable sequences; FK-16 (the core fragment of LL-37) retains substantial activity against MDR bacteria. Nanoparticle encapsulation using polymeric nanoparticles, liposomes, or hydrogels protects AMPs from proteolysis, extends half-life, and enables controlled local release at infection sites [28,30,31]. Lipidation (addition of fatty acid tails) increases membrane affinity and can convert shorter peptides to effective membrane-active agents.

AI-assisted AMP discovery: the emerging paradigm

The application of artificial intelligence and machine learning to AMP discovery represents a transformative development in the field. Santos-Júnior et al. deployed machine-learning models to analyze 87,920 metagenomes from 253 environments, identifying 863,498 putative AMP sequences [12] — massively expanding the known AMP sequence space beyond anything achievable by conventional biochemical screening. Li et al. demonstrated a deep learning 'foundation model' approach trained on diverse antibiotic-related sequences, predicting broad-spectrum AMPs active against MDR bacteria including carbapenem-resistant pathogens [13]. Wan et al. applied deep learning to identify AMPs from extinct organisms ('molecular de-extinction'), discovering structurally novel peptides with potent activity [14]. These AI approaches address the critical bottleneck of the traditional discovery pipeline — the empirical screening of vast sequence spaces — by providing computationally predicted candidates with target-optimized properties. The integration of generative AI models for de novo AMP design, combined with in vitro validation and pharmacokinetic optimization, is anticipated to substantially accelerate clinical translation in the coming decade [12-14].

Five Key Clinical Points for Clinical Practice

1. AMP deficiency is a clinically actionable mechanistic explanation for infection susceptibility in atopic dermatitis. The recurrent *S. aureus* superinfections in AD — and the risk of eczema herpeticum — are not simply consequences of barrier dysfunction but reflect profound suppression of LL-37 and hBD-2/3 by the Th2 cytokine environment [7,8,21]. Dupilumab (anti-IL-4Rα), by restoring Th1/Th17 balance, partially reverses this AMP suppression. Systemic vitamin D supplementation (which induces CAMP/LL-37 via VDRE) represents an additional mechanistic strategy, particularly in D-deficient patients with severe AD [10,11].

2. Psoriatic skin is microbiologically protected — the corollary of excess LL-37 production. Clinicians should recognize that while the excess LL-37 in psoriasis drives pathological type I interferon activation, it simultaneously confers robust

Table 4: Clinical pipeline of antimicrobial peptides: approved agents and compounds in advanced clinical development (2024) (Data from: ClinicalTrials.gov, [32]).

AMP / Compound	Origin / Class	Phase	Indication	Mechanism	Current status / Key data (2024)
Polymyxin B / E (colistin)	Bacillus polymyxa / lipopeptide	APPROVED	MDR Gram-negative infections (*P. aeruginosa, A. baumannii, K. pneumoniae*)	Membrane disruption (LPS binding)	FDA/EMA approved. Last-resort treatment for carbapenem-resistant Enterobacteriaceae (CRE). Nephrotoxicity limits use. New analogues (SPR206, murepavadin) in development to improve safety profile.
Daptomycin	Streptomyces roseosporus / cyclic lipopeptide	APPROVED	Complicated skin/ soft tissue infections; *S. aureus* bacteremia; right-sided endocarditis	Calcium-dependent membrane depolarisation (Gram-positive only)	FDA approved 2003. Widely used for MRSA and VRE infections. Resistance documented via MprF mutations (increased phosphatidylglycerol synthesis). Inactivated by pulmonary surfactant — cannot be used for pneumonia.
Rezafungin	Cyclic echinocandin lipopeptide	APPROVED (2023)	Invasive candidiasis / candidemia	β-1,3-glucan synthase inhibition (cell wall)	FDA approved March 2023. Once-weekly IV dosing. Phase III ReSTORE trial: non-inferior to caspofungin for candidiasis. Improved stability vs anidulafungin. First echinocandin approval in > 10 years.
Omiganan (CLS001)	Bovine indolicidin analogue / cationic	Phase II / III ongoing	Rosacea; acne vulgaris; atopic dermatitis; HPV-induced genital lesions; catheter infections	Membrane disruption + immunomodulation	Phase IIIb catheter UTI (S. aureus) failed. Phase III rosacea and Phase II atopic dermatitis ongoing. Phase II HPV genital lesions (2020): favourable safety profile. Prototype 12-aa analogue of indolicidin with enhanced stability.
Pexiganan (MSI-78, Locilex)	Magainin II analogue (Xenopus) / α-helical	Phase III (failed primary endpoint)	Mild diabetic foot ulcer infections	Membrane disruption (toroidal pore)	Phase III trials NCT01590758/NCT01594762: failed primary endpoint (non-inferior to vehicle + SOC). Higher-than-expected SAEs (osteomyelitis, cellulitis). Additional studies planned for surgical wounds, burns, decubitus ulcers. First major AMP Phase III in diabetes.
Brilacidin (PMX-30063)	Defensin-mimetic arylamide / synthetic	Phase II completed	Acute bacterial skin and skin-structure infections (ABSSSIs); COVID-19 (exploratory)	Membrane disruption (defensin-like); anti-inflammatory	Phase 2a/2b for ABSSSI (MRSA): non-inferior to daptomycin in small trials. Explored as COVID-19 adjunct (2020–2021). Synthetic small molecule (not peptide), less susceptible to proteolysis. Phase III initiation pending funding.
LL-37 (CAP-18 derived)	Human cathelicidin / α-helical	Phase I/II completed	Venous leg ulcers; melanoma (intratumoral)	Membrane disruption + wound healing + immunomodulation	Phase II venous leg ulcers (NCT00659048): improved healing vs placebo. Phase I/II melanoma completed 2024: safe via intratumoral injection; tumour microenvironment modulation with enhanced immune infiltration (Zheng et al., 2025). FDA wound-healing application.
NP213 (Novexatin)	Cyclic cationic peptide / synthetic	Phase II completed	Onychomycosis (fungal nail infection)	Membrane disruption; nail penetration	Phase II: significant efficacy against Trichophyton rubrum; excellent nail penetration. Well tolerated. Water-soluble cyclic structure resists proteolysis. Phase III design pending.
Murepavadin (POL7080)	β-hairpin peptidomimetic / synthetic	Phase III (halted 2019)	*P. aeruginosa nosocomial pneumonia*	LptD (lipopolysaccharide transport) inhibitor — novel non-membrane target	Phase III PRISM-MDR (NCT02096328): halted early due to excess nephrotoxicity in combination with standard-of-care. Potent in vitro vs P. aeruginosa (MIC 0.06–0.125 mg/L). New formulations under investigation to reduce renal burden.
DPK-060	Kininogen-derived cationic peptide	Phase II completed	Atopic dermatitis; acute otitis externa	Broad-spectrum membrane disruption	Phase II atopic dermatitis (NCT01522391) and acute otitis externa (NCT01447017): safety and efficacy demonstrated. 20-aa cationic peptide derived from human plasma kininogen domain. Well tolerated topically.

ABSSSI = Acute bacterial skin and skin-structure infections; CRE = Carbapenem-resistant Enterobacteriaceae; EMA = European Medicines Agency; FDA = US Food and Drug Administration; HPV = Human papillomavirus; IV = Intravenous; MDR = Multidrug-resistant; MIC = Minimum inhibitory concentration; MRSA = Methicillin-resistant *S. aureus*; SAE = Serious adverse event; SOC = Standard of care; VRE = Vancomycin-resistant enterococcus.

antimicrobial protection [6,11]. Psoriatic plaques rarely become superinfected — unlike AD lesions. Biologics targeting the IL-17 and IL-23 axis in psoriasis should not be expected to increase infection susceptibility via AMP suppression, as the dominant Th1 and Th17 environments of psoriasis independently support hBD-2/3 expression.

3. NOD2 mutation genotyping in Crohn's disease has direct implications for Paneth cell AMP biology. NOD2/CARD15 loss-of-function variants (R702W, G908R, 1007fs) significantly impair Paneth cell HD-5/HD-6 secretion [19,20]. Clinically, this translates to deficient small intestinal antimicrobial protection and a microbiome dysbiosis that contributes to the ileal predominance and recurrence pattern of Crohn's disease in NOD2-positive patients. Restoring antimicrobial mucosal defense — through microbiome modulation, exclusive enteral nutrition, or future Paneth cell-directed AMP delivery strategies — addresses a fundamental pathophysiological deficit [20].

4. Vitamin D status is a modifiable determinant of innate antimicrobial defense. The CAMP gene contains a well-characterized VDRE, making LL-37 expression directly inducible by 1,25-dihydroxyvitamin D3 [10,11,23]. Populations with chronic vitamin D deficiency (elderly, institutionalized, melanized skin, malabsorptive states, and high latitude) have measurably lower baseline LL-37 levels and greater susceptibility to respiratory pathogens, skin infections, and severe COVID-19. Vitamin D correction does not replace antibiotics for established infections but is a rational adjunct to AMP-dependent innate defense, particularly in at-risk groups [10].

5. Approved AMP-based drugs are already in clinical practice — the pipeline is not purely experimental. Polymyxin B and colistin remain frontline last-resort options for carbapenem-resistant Gram-negative infections. Daptomycin is a standard therapy for MRSA/VRE skin infections and bacteremia. Rezafungin (FDA March 2023) represents a significant once-weekly echinocandin option for invasive candidiasis [30,33,34]. The clinician should recognize that AMP-class drugs are not speculative future agents but a current part of the antimicrobial armamentarium, with a growing pipeline of second-generation agents addressing the limitations of existing drugs.

Conclusions

Antimicrobial peptides occupy a pivotal and multifunctional position at the interface of innate immunity, microbial defense, inflammatory regulation, and therapeutic development. The evidence reviewed leads to the following key conclusions, stratified by level of evidence.

Level A (replicated multicenter clinical/translational data): LL-37/hBD-2 deficiency in atopic dermatitis is mechanistically established and explains paradoxical infection susceptibility; IL-4/IL-13 suppression of CAMP/DEFB4 transcription is confirmed in multiple independent studies [7,8,21]. Paneth cell α-defensin (HD-5/HD-6) deficiency is a validated consequence of NOD2 mutations in ileal Crohn's disease and contributes to intestinal microbiome dysbiosis [19,20]. Three clinically used drugs — polymyxin B/colistin, daptomycin, and rezafungin (2023) — are AMP-class agents, confirming clinical proof-of-concept [33].

Level B (single-center or smaller confirmatory studies): LL-37-NET-DNA complexes are established activators of the type I interferon signature in SLE via pDC TLR9 activation [9]. CAMP gene VDRE-mediated LL-37 induction by vitamin D3 is established, with epidemiological correlations in respiratory infections and COVID-19 severity [10,23]. AI-driven AMP discovery has identified hundreds of thousands of putative novel AMP sequences, with initial laboratory validation showing potent broad-spectrum activity against MDR pathogens [12-14].

Level C (early-phase clinical data, single trials): brilacidin Phase II data suggest non-inferiority to daptomycin for ABSSSI; LL-37 intra-tumoral injection completed Phase I/II for melanoma (2024) with safety established and immunological activity observed. The combination of mechanistic clarity, clinical urgency driven by AMR, and technological momentum from AI-assisted discovery places the AMP field at an inflection point that warrants sustained investment and clinical engagement [30,33,34].

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