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The Vitamin D-Antimicrobial Peptide Axis in Host Defense Against Parasitic Infections, with a Focus on Protozoa

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Abstract

Parasitic diseases, especially those caused by protozoa, continue to pose a significant global health challenge, further exacerbated by rising drug resistance and limited vaccine availability. Concurrently, vitamin D has been identified as a critical immunomodulator influencing both innate and adaptive immune responses, partly through the regulation of antimicrobial peptides (AMPs) such as cathelicidin (LL-37) and specific defensins in immune and epithelial cells. This review evaluates the "vitamin D–AMP axis" as a potential mechanism of host defense against parasitic infections, with a particular focus on protozoan pathogens. The review first outlines vitamin D metabolism, vitamin D receptor (VDR) signaling, and the molecular mechanisms underlying AMP induction. It then summarizes AMP families, their regulatory pathways, and their direct as well as immunomodulatory antiparasitic activities. Subsequently, the available evidence regarding the vitamin D–AMP axis in specific infections, including Leishmania, Plasmodium, Toxoplasma gondii, Cryptosporidium parvum, Giardia duodenalis, and Entamoeba histolytica, is synthesized. Mechanistic evidence is most robust for Leishmania, where VDR-dependent cathelicidin facilitates macrophage-mediated parasite control and is actively targeted by parasite evasion strategies. In contrast, evidence for other protozoan infections is primarily associative or inferential. Finally, the review addresses clinical and translational implications, including the potential of vitamin D as a host-directed adjunct and the development of AMP-based therapeutics.

Keywords: Vitamin D; Antimicrobial peptides; Cathelicidin; Defensins; Protozoa; Parasites; Host defense; Immunity.
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1. Introduction

Protozoan and other parasitic infections continue to cause significant morbidity and mortality worldwide, especially in low- and middle-income countries. Global estimates indicate that food- and vector-borne parasitic diseases, such as toxoplasmosis and various helminthiases, are responsible for millions of disability-adjusted life years (DALYs) annually.[1,2] Among protozoa, malaria, leishmaniasis, trypanosomiases, amoebiasis, giardiasis, and cryptosporidiosis are major public health concerns. These infections often coexist with malnutrition, HIV infection, and other comorbidities that further compromise host immunity.[3-5] Although advances have been made in vector control and chemotherapeutic interventions, most parasitic diseases still lack effective vaccines, and the emergence of drug resistance highlights the urgent need to elucidate host-directed defence mechanisms.

The innate immune system serves as the primary defense against parasitic invasion, integrating physical barriers, soluble mediators, and cellular responses. Epithelial surfaces of the skin, gut, and respiratory tract provide not only mechanical protection but also secrete antimicrobial peptides (AMPs), while underlying phagocytes and other leukocytes rapidly respond to pathogen-associated molecular patterns.[6-8] AMPs, including cathelicidins and defensins, are small cationic peptides with broad-spectrum activity against bacteria, fungi, and enveloped viruses, and represent conserved elements of vertebrate host defense.[9,10] In addition to their direct microbicidal properties, AMPs function as immunomodulators by promoting chemotaxis, modulating Toll-like receptor (TLR) signaling, and influencing cytokine production, thereby shaping both innate and adaptive immune responses.[11-13] Most mechanistic studies have focused on bacteria and viruses. However, AMPs also act against

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protozoan parasites, including *Leishmania* spp., *Plasmodium* spp., *Toxoplasma gondii*, *Cryptosporidium parvum* and several intestinal protozoa, underlining their potential role in antiparasitic immunity.

Vitamin D, traditionally recognized for its role in calcium homeostasis and bone health, is now established as a key immunomodulatory hormone. The active metabolite 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) is synthesized not only in the kidney but also locally by immune and epithelial cells expressing the activating enzyme 1α-hydroxylase (CYP27B1).[14-16] The vitamin D receptor (VDR), a ligand-activated transcription factor, is broadly expressed in monocytes/macrophages, dendritic cells, neutrophils, and T and B lymphocytes, where its activation modulates cell differentiation, cytokine profiles, and effector functions.[15,17,18] These actions enable vitamin D to limit excessive inflammation while maintaining pathogen control, a balance that is particularly important in chronic and tissue-destructive parasitic infections.

One of the primary mechanisms by which vitamin D enhances innate defense is through the regulation of AMP expression. Foundational studies demonstrated that $1,25(OH)_2D_3$ induces the human cathelicidin antimicrobial peptide (CAMP) gene via a functional vitamin D response element (VDRE) in its promoter, which is directly bound by the VDR-RXR complex.[19] Comparable vitamin D-dependent regulation has been observed for certain β-defensin genes in epithelial and immune cells, establishing a link between vitamin D status and AMP levels at barrier sites.[20,21] In humans and other primates, Toll-like receptor (TLR) activation in macrophages or epithelial cells can upregulate CYP27B1 and VDR, thereby facilitating local conversion of 25-hydroxyvitamin D_3 to $1,25(OH)_2D_3$ and subsequent induction of cathelicidin and defensins. This pathway is commonly referred to as the vitamin D-AMP or vitamin D-cathelicidin axis.[20,22,23]

The vitamin D-AMP axis has been extensively investigated in bacterial, viral, and more recently, fungal infections, where vitamin D-induced cathelicidin and β-defensins can directly eliminate pathogens, enhance phagocyte function, and modulate inflammatory responses.[13,24,25] In contrast, the role of this axis in resistance or susceptibility to parasitic diseases remains less well understood. Recent evidence indicates that vitamin D status and VDR signaling can affect outcomes in malaria, leishmaniasis, toxoplasmosis, and intestinal protozoan infections, and that AMPs exhibit antiparasitic activity in several of these contexts. Nevertheless, direct mechanistic connections among vitamin D, AMP induction, and parasite control are still incomplete, and in some experimental models, vitamin D appears to have complex or even paradoxical effects on infection and pathology.

This review aims to synthesize current knowledge regarding the vitamin D-AMP axis in the context of parasitic infections, with a particular focus on protozoa. Following a brief overview of vitamin D biology, AMP families, and their regulation, the review examines evidence for vitamin D-dependent AMP responses in major protozoan diseases, including *Plasmodium, Leishmania, Toxoplasma, Cryptosporidium, Giardia,* and *Entamoeba* infections. By integrating findings from cellular, animal, and human studies, the review seeks to identify where this axis is relevant for host defense, where evidence remains conflicting or incomplete, and how improved understanding of vitamin D-induced AMPs could inform future host-directed therapies against parasitic diseases.

2. Vitamin D biology in the context of immunity

Within the immune system, vitamin D acts primarily as a locally activated, transcriptionally active hormone rather than solely as a systemic nutrient. Circulating vitamin D_3 or D_2 is metabolized in the liver to 25-hydroxyvitamin D (25(OH)D), which serves as the principal reservoir. Traditionally, renal 1α-hydroxylase (CYP27B1) converts 25(OH)D to the active metabolite 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). However, numerous extra-renal cell types, including macrophages, dendritic cells, and epithelial cells, also express CYP27B1 and can generate $1,25(OH)_2D$ through autocrine or paracrine mechanisms.[26-28] In these immune and barrier cells, CYP27B1 is regulated mainly by pattern-recognition receptor signalling and inflammatory cytokines, rather than by calcium and parathyroid hormone. This regulation couples $1,25(OH)_2D$ production directly to infection and tissue injury.[16,29]

The biological actions of $1,25(OH)_2D$ are mediated by the vitamin D receptor (VDR), a nuclear receptor broadly expressed in both innate and adaptive immune cells. Upon ligand binding, VDR forms a heterodimer with retinoid X receptor (RXR), binds to VDREs in target gene promoters, and regulates the transcription of numerous genes involved in cell differentiation, cytokine signalling, pattern-recognition pathways, and antimicrobial defense.[30-32] In immune cells, the same intracrine system responsible for generating $1,25(OH)_2D$

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also induces CYP24A1, the inactivating 24-hydroxylase, thereby establishing a local negative feedback loop that restricts the duration of vitamin D signalling without necessarily affecting systemic hormone concentrations.[31,33,34] This regulatory framework enables vitamin D to function as a context-dependent modulator of immune responses rather than as a binary switch.

At the level of innate immunity, vitamin D has prominent effects on mononuclear phagocytes, dendritic cells and neutrophils. In monocytes and macrophages, $1,25(OH)_2D$ promotes differentiation, enhances phagocytic capacity, and modulates pattern-recognition receptor pathways; it generally reduces expression of pro-inflammatory cytokines such as IL-12, IL-6 and TNF-α while favouring IL-10 production.[15,16,35] Dendritic cells exposed to $1,25(OH)_2D$ adopt a more "tolerogenic" phenotype, with reduced costimulatory molecule expression and altered cytokine output, which in turn shapes downstream T cell responses.[32,36] Neutrophils and other granulocytes also express VDR and CYP27B1, and vitamin D signalling influences their oxidative burst, survival and production of antimicrobial mediators, though these effects appear to be context and tissue-specific[15,37] Collectively, these actions tend to enhance microbicidal functions while constraining excessive inflammation.

Vitamin D also exerts significant control over adaptive immunity. In T cells, $1,25(OH)_2D$ dampens T helper 1 (Th1) and Th17 responses and favours the development of regulatory T cells (Tregs), partly through indirect effects on antigen-presenting cells and partly through direct VDR-dependent signalling in T lymphocytes[14,32,36] These shifts can decrease IFN-γ and IL-17 production while promoting IL-10, altering the balance between inflammatory and regulatory responses that is critical in chronic infections and immunopathology. In B cells, vitamin D limits proliferation and plasma-cell differentiation and can modulate immunoglobulin production, contributing further to the overall tuning of adaptive immunity.[15]

A critical aspect of host-parasite interactions is the influence of vitamin D signalling at epithelial and mucosal barriers. VDR is abundantly expressed in keratinocytes as well as intestinal and respiratory epithelial cells, where $1,25(OH)_2D$ regulates tight junction proteins (occludin, claudins, ZO-1), cytoskeletal organization, apoptosis, and autophagy.[38-41] These processes enhance barrier integrity, affect interactions with the microbiota, and modulate the exposure of underlying immune cells to luminal antigens and pathogens. In the gut and skin, vitamin D/VDR signalling is closely integrated with transcriptional programs that control antimicrobial and host-defence peptide expression, often through, thereby linking barrier structure to chemical defense.[42-44]

Collectively, these metabolic, transcriptional, and tissue-specific characteristics illustrate how vitamin D serves as a nuanced regulator of immunity. This framework underpins its more specialized role in controlling antimicrobial peptides at barrier sites and within phagocytes during parasitic infection.

3. Antimicrobial peptides: families, regulation, and functions

Antimicrobial peptides (AMPs), also known as host-defence peptides, are short, typically cationic molecules produced by diverse organisms, ranging from bacteria to humans. These peptides generally consist of approximately 10 to 50 amino acids, form amphipathic structures, and function both as direct microbicidal agents and as regulators of immune responses.[45-47] In vertebrates, AMPs are prevalent at epithelial surfaces and within leukocyte granules, where they facilitate rapid, non-specific containment of invading microbes, including protozoan parasites.

3.1 Major AMP families relevant to parasitic infections

Among the various AMP classes, cathelicidins and defensins are the most extensively characterized in mammals and are particularly significant in host-parasite interactions. Cathelicidins are synthesized as prepro-proteins with an N-terminal cathelin domain and a C-terminal antimicrobial domain, the latter being released through proteolysis. The human cathelicidin LL-37 is a 37-residue, α-helical, amphipathic peptide with a net positive charge, which facilitates binding to negatively charged microbial surfaces and membrane insertion.[48-50] Homologues such as mouse cathelicidin-related antimicrobial peptide (CRAMP) exhibit comparable structural and functional characteristics.

Defensins constitute another large family of cysteine-rich, β-sheet peptides, subdivided into α-, β- and θ-defensins. They are stabilized by three intra-molecular disulfide bonds and display potent activity against bacteria, fungi and many viruses[51,52] In humans, α-defensins are highly expressed in neutrophil granules (HNP-1-4) and Paneth cells of the small intestine (HD-5, HD-6), whereas β-defensins are produced by epithelial cells at skin and mucosal surfaces.[53]

In addition to cathelicidins and defensins, several other AMP families contribute to antiparasitic defense. Amphibian skin peptides (such as magainins, temporins, and phylloseptins), arthropod venom peptides, and plant- or fungal-derived defensin-like molecules have demonstrated

activity against protozoa including *Plasmodium, Leishmania,* and *Trypanosoma*[54-57] The structural diversity of these peptides expands the spectrum of potential AMP-parasite interactions and offers templates for therapeutic development.

3.2 Regulation of AMP expression

AMP production is stringently regulated by both local and systemic signals, enabling barrier tissues to adapt to environmental challenges. Pattern-recognition receptor signaling, such as through Toll-like receptors or NOD-like receptors, and pro-inflammatory cytokines including IL-1β and TNF, can rapidly induce AMP expression in epithelial and myeloid cells.[45,52,53] At mucosal surfaces, type 17 cytokines (IL-17A/F) and IL-22, produced by Th17 cells and group 3 innate lymphoid cells, are especially critical in driving AMP production and coordinating epithelial responses to infection.[58-60]

The intestinal microbiota adds another regulatory dimension by influencing baseline AMP expression and responsiveness. Signals derived from commensal organisms help sustain constitutive defensin and cathelicidin production in the gut, thereby promoting spatial segregation of microbes and restricting the proliferation of pathobionts.[53,60] During infection with enteric protozoa such as *Giardia*, epithelial AMP output may change further and can increase protection against co-infecting bacteria through higher secretion of β-defensins and trefoil factor 3.[58,61,62] Endocrine and metabolic factors, including micronutrients and hormones, also modulate AMP gene transcription, thereby linking nutritional status to barrier defense.[53,63]

3.3 Mechanisms of action and immunomodulatory roles

Traditionally, AMPs exhibit direct microbicidal activity by targeting microbial envelopes. Many cationic peptides bind to negatively charged phospholipids, aggregate on the microbial surface, and insert into membranes, resulting in pore formation or non-specific membrane thinning and disruption.[49,64] Some AMPs translocate into the cytosol, where they disrupt nucleic acid synthesis, protein folding, or enzyme activity. These mechanisms of membrane permeabilization and intracellular targeting are also applicable to unicellular eukaryotes, which may experience altered membrane potential, osmotic imbalance, and organelle dysfunction in response to AMPs.[57,65]

The immunomodulatory functions of AMPs are equally significant. LL-37 and several defensins serve as chemoattractants for neutrophils, monocytes, and T cells, modulate dendritic cell maturation, and can either enhance or suppress inflammatory responses depending on the context.[53,60] AMPs also bind to microbial products such as lipopolysaccharide, neutralizing their pro-inflammatory effects, and contribute to processes including wound healing, angiogenesis, and regulation of epithelial proliferation.[45,46,66] In the gastrointestinal tract, defensins and related peptides shape the composition of the microbiota, thereby indirectly affecting susceptibility to both bacterial and protozoan pathogens.[53,67]

3.4 AMPs in protozoan parasitic infections

In protozoan infections, AMPs exert both direct and indirect effects. Experimental studies demonstrate that various cathelicidins, defensins, and venom-derived peptides disrupt membranes, depolarize mitochondria, or interfere with essential metabolic pathways in *Leishmania, Plasmodium, Trypanosoma, Cryptosporidium, Giardia,* and *Entamoeba* species.[54,68-71] Concurrently, AMPs influence the host response by promoting the recruitment and activation of phagocytes, modulating cytokine environments, and strengthening epithelial barriers at sites of parasite attachment, invasion, or replication.[53,58,59,72] Protozoan parasites can evade these defenses by secreting proteases that degrade defensins and related peptides or by modifying host signaling pathways that regulate AMP expression.[73-75]

In summary, AMPs represent a structurally diverse and tightly regulated network of molecules that not only exert direct antimicrobial effects but also coordinate broader immune and barrier responses. This complexity creates multiple opportunities for upstream regulators, such as nutritional and hormonal signals, to modulate antiparasitic defense. This concept is particularly relevant when examining the vitamin D-AMP axis in subsequent sections.

4. The Vitamin D-AMP axis

The vitamin D-AMP axis describes a tightly integrated pathway in which vitamin D signaling directly regulates AMP gene expression and is further coordinated with pattern-recognition and cytokine networks. This axis is most thoroughly characterized for cathelicidin and selected β-defensins, and exhibits notable species restriction, with pronounced effects in humans and other primates.[19,23,25] The main AMP families and their relationship to vitamin D signalling in humans and mice are summarized in Table 1.

4.1 Direct transcriptional coupling of VDR to AMP genes

The human cathelicidin gene CAMP serves as the prototypical example. A functional VDRE within the CAMP promoter is bound by the liganded VDR-RXR complex, and 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) strongly induces CAMP

Table 1: Representative studies defining the vitamin D-AMP axis.

AMP(s)	Model / system	Vitamin D manipulation	Main findings on the vitamin D-AMP axis	Refs.
LL-37 (CAMP), HBD-2 (DEFB4)	Primary human keratinocytes, monocytes, neutrophils; human cell lines	$1,25(OH)_2D_3$ *in vitro* ± LPS	Identified functional VDREs in CAMP and DEFB4 promoters; $1,25(OH)_2D_3$ induces AMP mRNA/protein and antimicrobial activity against *Pseudomonas aeruginosa*, establishing vitamin D as a direct transcriptional inducer of AMP genes.	[76]
LL-37 (CAMP)	Human AML cells, keratinocytes, colon cells, BM macrophages; murine BM (WT, $VDR^{-/-}$)	$1,25(OH)_2D_3$ and analogs *in vitro*; VDR binding and cross-species comparison	$1,25(OH)_2D_3$ strongly induces human CAMP via a consensus VDRE; murine *Camp* is not vitamin D–responsive and is unchanged in $VDR^{-/-}$ BM, indicating primate-specific vitamin D regulation of cathelicidin.	[19]
LL-37	Primary human monocytes/macrophages infected with *M. tuberculosis*	TLR2/1 ligand stimulation ± physiological 25(OH)D; exogenous $1,25(OH)_2D_3$	TLR2/1 activation upregulates VDR and CYP27B1, driving conversion of 25(OH)D to $1,25(OH)_2D_3$, induction of cathelicidin, and killing of intracellular *M. tuberculosis*; low serum 25(OH)D impairs cathelicidin induction and antimycobacterial activity, defining the TLR-vitamin D-cathelicidin axis.	[77]
LL-37	Human THP-1 monocytic cells infected with *M. tuberculosis* H37Ra	$1,25(OH)_2D_3$ ± cathelicidin-specific siRNA	$1,25(OH)_2D_3$ induces cathelicidin and restricts intracellular *M. tuberculosis* growth; cathelicidin knockdown abrogates vitamin D-mediated killing, showing cathelicidin is required for vitamin D-triggered antimycobacterial activity.	[78]
LL-37	Primary normal and CF human bronchial epithelial cells; airway surface fluid	$1,25(OH)_2D_3$ (10^{-8} M) ± high Ca^{2+}	$1,25(OH)_2D_3$ increases cathelicidin ≈10-fold in airway epithelium (normal and CF); Ca^{2+} co-treatment augments this further and enhances killing of *Bordetella bronchiseptica* and *Pseudomonas aeruginosa*, extending the VD-cathelicidin axis to airway mucosa.	[79]
LL-37	Human keratinocytes; human skin wounds; $CYP27B1^{-/-}$ vs WT mice	TGF-β_1 + $25(OH)D_3$; low-dose $1,25(OH)_2D_3$; topical $1,25(OH)_2D_3$; CYP27B1 inhibition/knockout	Skin injury and TGF-β_1 increase keratinocyte CYP27B1, generating local $1,25(OH)_2D_3$ that induces cathelicidin, CD14, and TLR2; blocking CYP27B1 or VDR prevents AMP induction. In mice, CD14 but not *Camp* depends on CYP27B1, further highlighting species-specific VD control of AMPs and a VDR-driven AMP response during wound repair.	[80]
HBD-2 (DEFB4), LL-37	Primary human monocytes	$1,25(OH)_2D_3$; TLR2/1 ligand; VDR antagonist; IL-1β neutralization	$1,25(OH)_2D_3$ alone induces cathelicidin but not DEFB4; TLR2/1 stimulation upregulates both. TLR-induced DEFB4 requires VDR activation and IL-1β, as VDR antagonist or IL-1β blockade nearly abolish DEFB4, defining a TLR–IL-1β–vitamin D pathway for HBD-2 distinct from cathelicidin.	[81]
LL-37	Human monocytes/macrophages infected with *M. tuberculosis*	$1,25(OH)_2D_3$; cathelicidin and autophagy gene knockdown; autophagy inhibitors	$1,25(OH)_2D_3$ induces autophagy via cathelicidin-dependent upregulation of Beclin-1 and Atg5 and promotes colocalization of mycobacterial phagosomes with autophagosomes; vitamin D-mediated killing of *M. tuberculosis* requires both cathelicidin and autophagy, linking AMPs to non-canonical effector pathways.	[82]

AMP(s)	Model / system	Vitamin D manipulation	Main findings on the vitamin D-AMP axis	Refs.
Paneth α-defensins (DEFA5, murine cryptdins)	Mice on high-fat diet (HFD) ± vitamin D deficiency; global VDR$^{-/-}$ mice; DEFA5 supplementation	Dietary vitamin D deficiency; VDR knockout; oral DEFA5	HFD plus vitamin D deficiency markedly suppresses ileal α-defensins, MMP7, tight junction genes and MUC2, causing barrier failure, dysbiosis, endotoxemia, systemic inflammation, insulin resistance and fatty liver; VDR$^{-/-}$ mice show similar changes. Oral DEFA5 restores eubiosis and metabolic phenotype, implicating a VDR-Paneth defensin axis in gut and systemic homeostasis.	[83]
Paneth lysozymes and granule AMPs	Crohn's disease small-intestinal biopsies; Paneth cell-specific VDRΔPC mice	Paneth cell-specific VDR deletion; correlative analysis of VDR in CD	In CD patients, reduced VDR correlates with decreased ATG16L1 and Paneth lysozymes. VDRΔPC mice show reduced lysozyme expression, abnormal Paneth granules, impaired bacterial killing and heightened inflammation after *Salmonella* or NSAID injury, indicating Paneth cell VDR as a tissue-specific gatekeeper of antimicrobial function and inflammatory threshold.	[84]
LL-37 (CAMP)	Comparative genomics; reporter assays in human cells	Functional analysis of VDRE within primate-specific AluSx element; $1,25(OH)_2D_3$-responsive reporters	Demonstrated that a primate-specific Alu SINE upstream of CAMP contains a VDRE that confers vitamin D responsiveness; non-primate mammals lack this element. Provides evolutionary evidence that VD-inducible cathelicidin is a primate innovation driven by an exapted transposable element.	[85]
Human LL-37 (CAMP) transgene; murine CRAMP	CAMP-transgenic mice on a *Camp*$^{-/-}$ background; wound and *Salmonella* models	Topical $1,25(OH)_2D_3$ to skin; TLR activation ± $25(OH)D_3$	Human CAMP transgene is broadly expressed; topical $1,25(OH)_2D_3$ induces CAMP in transgenic skin and enhances *Staphylococcus aureus* killing and wound healing; transgene reduces intestinal *Salmonella* colonization. TLR + $25(OH)D_3$ do not fully recapitulate human-like CAMP induction in murine macrophages, underscoring species constraints on the VD-cathelicidin axis despite a useful in vivo model.	[22]
LL-37 (CAMP/hCAP18)	Human PBMC from healthy donors; ex vivo stimulation with LPS or poly(I:C)	25(OH)D exposure/supplementation ex vivo	PBMC can locally activate vitamin D; 25(OH)D increases intracellular cathelicidin, but a clear rise in extracellular LL-37 and anti-infective activity appears only when cells are co-stimulated with bacterial or viral mimetics, showing that vitamin D potentiates stimulus-driven LL-37 release rather than acting as a stand-alone trigger.	[86]
LL-37	Bladder biopsies from postmenopausal women before/after $25(OH)D_3$ supplementation; human bladder epithelial cell lines	Oral $25(OH)D_3$ (12 weeks) *in vivo;* $1,25(OH)_2D_3$ *in vitro; ex vivo* infection with uropathogenic *E. coli*	$25(OH)D_3$ supplementation raises serum 25(OH)D but does not increase bladder cathelicidin at rest; after supplementation, E. coli–infected bladder biopsies show higher cathelicidin and antibacterial activity. In vitro, $1,25(OH)_2D_3$ directly induces cathelicidin and enhances killing of uropathogenic *E. coli*, extending the VD–cathelicidin axis to the urinary tract and highlighting its dependence on infection-associated signals.	[87]

expression in both myeloid cells and epithelial tissues.[19,22] This VDRE is located within a primate-specific Alu element, which accounts for the absence of cathelicidin induction by vitamin D in rodents.[22,23] A similar, though less potent, VDRE has been identified in the promoter of DEFB4A, which encodes human β-defensin-2 (HBD-2), allowing $1,25(OH)_2D_3$ to directly promote DEFB4A transcription under permissive conditions.[16]

Beyond these canonical VDRE-containing genes, vitamin D also regulates the transcription of several upstream modulators of AMP expression, such as the pattern-recognition receptor NOD2 and the cytokine IL-1β.[16,88,89]

Induction of NOD2 by vitamin D sensitizes cells to muramyl dipeptide, which subsequently acts synergistically with $1,25(OH)_2D_3$ to enhance DEFB4 and CAMP expression through NF-κB.[90,91] Therefore, vitamin D is integrated both at the level of AMP gene promoters and within the upstream signaling pathways that activate them.

4.2 Pattern-recognition-driven intracrine vitamin D activation

A key characteristic of this axis is the close association between AMP induction and local, intracrine vitamin D activation. TLR signaling in human monocytes and macrophages upregulates CYP27B1 (1α-hydroxylase) and VDR, thereby increasing the intracellular conversion of circulating 25(OH)D to $1,25(OH)_2D_3$.[22,52,92] The newly synthesized $1,25(OH)_2D_3$ subsequently acts in an autocrine fashion to induce CAMP and, with appropriate co-stimulation, DEFB4A. This mechanism was initially described in TLR2/1-activated macrophages responding to mycobacterial ligands, but has since been observed in epithelial cells of the skin, lung, and gut, as well as in other TLR and NOD pathways.[25,34,52,92]

Epithelial injury and inflammatory signals further enhance this regulatory circuit. Factors such as TGF-β, IFN-γ, and IL-13 can upregulate CYP27B1 or VDR expression in keratinocytes or airway epithelial cells, thereby increasing vitamin D-induced CAMP production. In contrast, IL-10 and fibroblast growth factor 23 (FGF23) suppress CYP27B1, thereby limiting AMP induction.[16,88] In the respiratory tract, vitamin D-induced IL-1β from macrophages stimulates IL-1 receptor-dependent DEFB4A production in adjacent epithelial cells, demonstrating how the axis operates beyond the initially activated cell through paracrine cytokine signaling.[89]

4.3 Functional outputs: from gene induction to effector programmes

At the effector stage, the vitamin D-AMP axis contributes more than increased peptide levels. Vitamin D-induced cathelicidin initiates autophagy and enhances phagolysosomal fusion in monocytes and macrophages, thereby facilitating the clearance of intracellular pathogens.[25] HBD-2 and related defensins can modulate inflammasome and IL-1β pathways, linking vitamin D-mediated transcriptional changes to regulated inflammatory cell death and cytokine release.[16,52,89] In epithelial tissues, vitamin D-induced AMPs support wound healing, barrier restoration, and modulation of microbiota composition, resulting in an environment less conducive to colonization or invasion by pathogens, including protozoa.[23,25,34]

From a parasitological standpoint, these characteristics suggest that the vitamin D-AMP axis can affect infection at several levels: by directly damaging extracellular parasite stages, enhancing intracellular killing via autophagy-associated pathways, and modulating cytokine and chemokine environments that influence the balance between protective and pathogenic inflammation. The primate-specific nature of critical components of this axis, particularly the CAMP VDRE, indicates that its role in antiparasitic immunity may be underestimated in conventional rodent models. This limitation should be considered when extrapolating preclinical findings to human parasitic diseases.

4.4 Species differences and limitations of rodent models

A significant limitation in interpreting experimental data on the vitamin D-AMP axis is the existence of pronounced species differences. The most well-characterized example is the human cathelicidin gene CAMP, whose promoter contains a functional VDRE embedded within a primate-specific Alu short interspersed element.[19] Consequently, $1,25(OH)_2D_3$ robustly induces CAMP and LL-37 in human myeloid and epithelial cells, whereas the murine Camp gene lacks this VDRE and is largely unresponsive to vitamin D in conventional mouse strains.[20,22] Although murine cathelicidin (CRAMP) is structurally and functionally related to LL-37, its transcription is regulated by vitamin D-independent pathways. Therefore, standard rodent models do not accurately recapitulate the primate vitamin D-cathelicidin axis.[48,49] Humanized mouse models expressing a vitamin D-responsive human CAMP transgene partially address this limitation, but they represent only an approximation rather than a complete reconstruction of the human system.[22]

Species differences are also evident in intestinal Paneth-cell peptides. In humans, the primary α-defensins are HD-5 and HD-6, while mice express multiple cryptdins, which are not exact orthologues but share similar structural and functional properties.[83] Genetic and dietary studies in mice indicate that epithelial VDR signaling is necessary to maintain normal Paneth-cell α-defensin expression, lysozyme content, and granule morphology. Vitamin D or VDR deficiency results in reduced defensins, compromised barrier function, and dysbiosis, which can be mitigated by exogenous defensin supplementation.[84] These findings support the existence of a VDR-Paneth cell axis; however, the quantitative relationship between vitamin D status and Paneth-cell defensins may vary between species due to differences in defensin gene repertoires and microbiota composition.[83]

Collectively, these examples demonstrate that rodent models are valuable for elucidating biological pathways, such as intracrine CYP27B1-VDR signaling and Paneth-cell VDR

functions. However, they possess inherent limitations in quantifying vitamin D-dependent cathelicidin responses and in extrapolating the extent of AMP modulation to humans. When interpreting antiparasitic studies in mice, particularly those involving Leishmania, malaria, or intestinal protozoa, it is crucial to recognize that key components of the vitamin D-AMP axis, especially VD-inducible LL-37, are primate-specific and may have a greater impact on human infection than rodent data alone suggest.[22,48,85]

5. AMPs in antiparasitic host defense

Protozoan parasites present unique challenges to innate immunity compared to bacteria or fungi. As eukaryotes, they are typically larger and undergo multiple life stages, each characterized by distinct surface compositions and tissue niches. AMPs contribute to antiparasitic defense both as direct cytotoxic agents and as regulators of the mucosal microenvironment, inflammatory responses, and microbiota composition, thereby affecting parasite establishment and persistence (Fig. 1).

5.1 Protozoa as AMP targets: opportunities and obstacles

Protozoan membranes possess characteristics common to other eukaryotic cells, such as sterol-rich bilayers that can reduce AMP efficacy. However, they also display abundant anionic phospholipids on the outer leaflet, promoting interactions with cationic peptides.[65,68] Many parasites further enhance protection by developing additional layers. For example, cyst and oocyst forms of *Giardia, Entamoeba,* or coccidia form robust walls composed of glycoprotein, cross-linked protein, or chitin, which are poorly permeable to water-soluble agents and restrict AMP access. Flagellated forms like *Leishmania* promastigotes are enveloped in a dense glycocalyx, such as lipophosphoglycan, that can bind cationic AMPs and sequester them from the plasma membrane. Surface metalloproteases, including GP63, degrade peptide-based molecules.[93] These structural adaptations account for the wide variability in AMP susceptibility among parasite species and life-cycle stages.

5.2 Direct antiparasitic mechanisms

Despite these protective barriers, numerous AMPs exhibit significant activity against protozoa. Mechanistically, their actions resemble classic antibacterial models, including carpet-like surface disruption and barrel-stave or toroidal pore formation, but are adapted to the unique properties of parasite membranes. Amphibian peptides such as temporins, magainins, and cecropin-melittin hybrids, as well as mammalian cathelicidins, can depolarize protozoan membranes, disrupt ATP gradients, and induce osmotic lysis. These effects often display stage-specific susceptibility, with Leishmania promastigotes, for example, being more sensitive than amastigotes.[94,95]

In certain instances, AMPs access intracellular targets following initial membrane disruption. For example, the mouse Paneth-cell α-defensin cryptdin-2 eliminates *Entamoeba histolytica* trophozoites at concentrations similar to metronidazole, inducing extensive membrane damage, cytoplasmic leakage, and inhibition of DNA, RNA, and protein synthesis in a dose-dependent manner.[96] Comparable dual membrane and intracellular effects have been observed for AMPs targeting trypanosomatids and *Plasmodium* species, where peptides disrupt mitochondrial integrity, glycolytic enzymes, or other metabolic pathways.[65,68] These multi-target mechanisms are believed to decrease the likelihood of conventional drug resistance.

The antiparasitic potential of AMPs remains insufficiently investigated. Of nearly 3,000 natural AMPs identified, fewer than 100 have been systematically evaluated against protozoa. Most research has concentrated on *Plasmodium, Leishmania, Trypanosoma cruzi, Toxoplasma gondii,* and *Cryptosporidium*.[97]

5.3 Immunomodulatory and barrier-level roles

In addition to direct cytotoxicity, AMPs modulate host-parasite interactions by influencing both innate and adaptive immune responses. Cathelicidins and defensins function as chemoattractants, alter cytokine profiles, and promote autophagy and enhanced phagolysosomal fusion in myeloid cells.[98,99] During *Leishmania donovani* infection, exogenous human cathelicidin LL-37 decreases parasite survival in macrophages and increases IL-12 production, fostering a more protective inflammatory response.[68,100] Studies with synthetic and natural host defence peptides further demonstrate that their leishmanicidal effects are associated with alterations in macrophage activation states rather than membrane toxicity alone.[95,97]

At mucosal surfaces, AMPs coordinate barrier responses that indirectly affect protozoan colonization. In experimental models of Giardia co-infection, the parasite unexpectedly reduces colitis induced by attaching-and-effacing bacteria by stimulating epithelial secretion of β-defensin-2/3 and trefoil factor 3, thereby enhancing antibacterial defenses and limiting bacterial translocation. Paneth-cell α-defensins, such as cryptdins and human HD-5, modulate intestinal microbiota composition and restrict the overgrowth of pathobionts, which subsequently influences susceptibility to enteric parasites and the severity of tissue inflammation.[68,96]

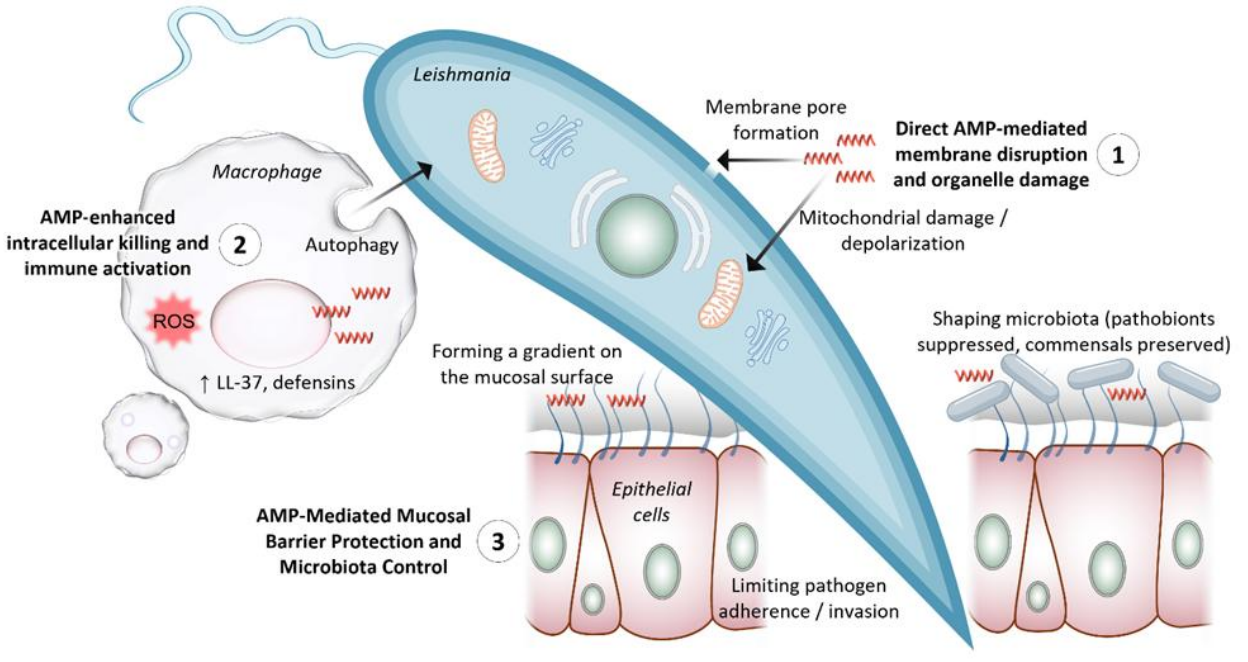

Fig. 1: Proposed mechanisms by which host antimicrobial peptides control protozoan parasites. (1) Direct AMP-mediated membrane and organelle damage. (2) AMP-dependent enhancement of intracellular killing and inflammatory signalling in infected macrophages. (3) AMP-driven barrier and microbiota protection at mucosal surfaces, limiting protozoan colonization. Graphic credit: Nuraly S. Akimbekov, 2025.

5.4 Parasite counter-measures

Protozoa have developed complex strategies to evade or counteract AMP-mediated defenses. Beyond physical barriers and surface proteases, some parasites secrete cysteine proteases that degrade host defensins, immunoglobulins, and chemokines, thereby diminishing both AMP-mediated cytotoxicity and leukocyte recruitment. Giardia intestinalis cysteine proteases can cleave human defensins and disrupt mucus and tight junction components, altering the epithelial environment to favor persistent colonization.[101-103] Leishmania can suppress host cathelicidin expression by interfering with vitamin D receptor signaling pathways, thereby reducing the efficacy of the AMP response during chronic infection.[68,100]

In summary, AMPs constitute a multi-layered defense system against protozoan parasites, integrating direct parasiticidal activity with significant effects on barrier integrity, microbiota composition, and immune cell function. Comprehending these principles is crucial for understanding how upstream regulators, such as vitamin D, modulate antiparasitic immunity through the AMP network.

6. Vitamin D-AMP Axis in specific parasitic infections

The general framework of vitamin D-driven AMP induction exhibits considerable variability across parasitic diseases. In certain infections, direct mechanistic evidence demonstrates that vitamin D modulates AMP expression and influences parasite control. In other cases, associations are indirect or inferred from epidemiological data and AMP biology. To complement the narrative synthesis below, we summarise the overall strength and nature of the evidence supporting a vitamin D-AMP axis in each major protozoan infection in Table 2, using a simple three-level grading (strong, moderate, weak) based on the presence of mechanistic data linking vitamin D/VDR to AMP induction and parasite control, supportive animal model findings, and human observational or interventional data.[65,70,104,105]

6.1 Kinetoplastids: leishmania spp

Among protozoan parasites, *Leishmania* offers the most compelling evidence that a vitamin D-AMP axis functions during infection. In human monocyte-derived macrophages infected with *Leishmania* spp., calcitriol upregulates CAMP transcription and cathelicidin protein, and this induction is necessary for optimal restriction of intracellular parasites.[104,105] Pharmacological activation of vitamin D signalling enhances leishmanicidal activity, while genetic or pharmacological inhibition of cathelicidin eliminates this

effect. These findings indicate that cathelicidin is a principal effector of vitamin D-mediated parasite control.[104,106]

Recent studies demonstrate that *Leishmania donovani* actively represses cathelicidin by inducing the transcriptional repressor CREM in infected macrophages. CREM reduces CAMP expression and promotes parasite survival.[107] As CAMP is a canonical VDR target, this repression represents a parasite strategy to disrupt the vitamin D-cathelicidin component of host defence. *In vivo*, observational data from canine leishmaniasis show that low serum 25(OH)D is associated with more advanced clinical disease, although correlations with parasite-specific cellular immunity are less consistent.[108,109] Collectively, these findings support a model in which vitamin D enhances cathelicidin-dependent killing of *Leishmania* in macrophages, while the parasite seeks to attenuate this axis at the transcriptional level.

6.2 Apicomplexa

In rodent models of malaria (*Plasmodium* spp.), vitamin D_3 and certain analogues consistently improve survival and reduce parasitaemia. In *Plasmodium chabaudi* – infected mice, vitamin D_3 treatment results in lower parasite burdens and increased survival, and a meta-analysis of multiple mouse studies confirms a beneficial effect on mortality.[110,111] These benefits are primarily attributed to the induction of nitric oxide and modulation of inflammatory cytokines. However, direct evidence that cathelicidin or defensins are essential for the antimalarial effect is lacking. One study reported that exogenous cathelicidin alone did not replicate the protection provided by vitamin D_3, suggesting that AMPs, if involved, function alongside other vitamin D-regulated pathways rather than as sole effectors.[110,112] Therefore, in malaria, the vitamin D-AMP axis remains mechanistically plausible but has not yet been demonstrated *in vivo*.

In experimental models of toxoplasmosis (*Toxoplasma gondii*), treatment with $1,25(OH)_2D_3$ reduces intracellular parasite replication and tissue parasite burden, yet treated animals may succumb earlier, indicating complex immunomodulatory effects.[113,114] *In vitro*, vitamin D_3 and IFN-γ act synergistically to inhibit parasite proliferation, partly through enhanced nitric oxide production in macrophages.[115] Large human datasets, such as NHANES-based analyses, reveal non-linear associations between serum 25(OH)D and *T. gondii* seropositivity, with both deficiency and very high levels linked to increased infection risk in some models. Several smaller studies associate vitamin D deficiency with more severe toxoplasmosis.[116-119] However, none of these investigations directly assess cathelicidin or defensins, leaving the role of the vitamin D-AMP axis in toxoplasmosis speculative.

In contrast, antimicrobial peptides are clearly involved in intestinal cryptosporidiosis (*Cryptosporidium parvum*). Neonatal mice, which depend heavily on CRAMP for mucosal defence, are highly susceptible to *C. parvum*, and sporozoites display marked sensitivity to CRAMP and several human β-defensins *in vitro*.[120-122] Administration of exogenous CRAMP reduces parasite load in infected neonates, yet the parasite actively subverts this defence by downregulating CRAMP expression in the ileal epithelium and differentially altering β-defensin transcripts.[122-125] Since cathelicidin and β-defensins are established vitamin D targets in human epithelium, these findings strongly suggest that a vitamin D-AMP axis may be important in cryptosporidiosis, although direct evidence from vitamin D supplementation or VDR-knockout experiments is currently lacking.

6.3 Intestinal protozoa: giardia and entamoeba

In *Giardia duodenalis* infection, AMP responses exhibit both protective and disease-modifying effects. Co-infection models demonstrate that *Giardia* can attenuate colitis caused by attaching-and-effacing bacteria by stimulating epithelial secretion of β-defensin-2/3 and trefoil factor 3 in an interleukin-22 (IL-22)- and NLRP3-dependent manner, thereby enhancing antibacterial defence and reducing epithelial damage.[58,61,62] Concurrently, *Giardia* secretes cysteine proteases and other excretory–secretory products that degrade human defensins (HBD-1, HD-6), chemokines (such as CXCL8 and CCL20), and mucins, disrupt tight junctions, and impair neutrophil recruitment. These strategies weaken AMP-mediated defences and facilitate persistent colonization.[74,101,102,126] Chronic giardiasis is often associated with fat-soluble vitamin deficiencies, including vitamin D, due to malabsorption. However, no study has directly examined whether correcting vitamin D status restores AMP profiles or influences parasite burden.

In *Entamoeba histolytica* infection, Paneth-cell α-defensins serve as key effector molecules. Cryptdin-2 exhibits potent amoebicidal activity at low micromolar concentrations, inducing membrane disruption, leakage of intracellular contents, and death of trophozoites in vitro, and confers protection against experimental amebic colitis in mice.[96] Infection alters Paneth-cell granule morphology and AMP expression, indicating that E. histolytica can disrupt this defensive compartment at the ileal level.[127,128] Given the established dependence of Paneth-cell defensins on epithelial VDR signalling in other contexts, it is plausible that vitamin D status modulates resistance to amebiasis via this pathway, although direct experimental evidence is lacking.

Collectively, these examples demonstrate a spectrum of involvement of the vitamin D-AMP axis in protozoan infections, ranging from well-supported, cathelicidin-centred mechanisms in *Leishmania* to more circumstantial or theoretical roles in malaria, toxoplasmosis, and intestinal protozoa. This heterogeneity highlights the necessity for parasite- and tissue-specific studies that concurrently assess vitamin D metabolites, VDR signalling, AMP expression, and parasitological outcomes.

7. Integrative perspective: synthesis of current evidence

Collectively, current evidence positions the vitamin D-AMP axis as a plausible, though not yet fully characterized, component of antiparasitic immunity. Mechanistically, this pathway is well established: in humans, $1,25(OH)_2D_3$-VDR signaling directly induces *CAMP* (LL-37) and supports *DEFB4A* (HBD-2) transcription in myeloid and epithelial cells, contributing to antibacterial and antiviral host defense both in vitro and *in vivo*.[16,19,20,25] Concurrently, an expanding body of literature demonstrates that AMPs, including cathelicidins, defensins, and a diverse array of venom- and amphibian-derived peptides exhibit potent activity against various protozoan genera and life-cycle stages.[100]

In the context of parasitic infections, the strength of evidence supporting the vitamin D-AMP axis varies significantly by pathogen. This heterogeneity is summarised in Table 2, which grades the overall strength and nature of the supporting data for each major protozoan infection. For *Leishmania*, direct evidence demonstrates that vitamin D–induced cathelicidin contributes to parasite control in human macrophages: pharmacological activation of VDR increases CAMP expression and restricts intracellular parasites, whereas RNAi-mediated cathelicidin knockdown reverses this effect (PMC). Additionally, recent studies indicate that the parasite up-regulates CREM to repress CAMP, suggesting a targeted immune-evasion strategy.[100] In contrast, for malaria and toxoplasmosis, vitamin D modulates disease outcomes improving survival or altering pathology in rodent models and correlating with serostatus or severity in humans, yet these effects are primarily attributed to changes in cytokines, nitric oxide, or T-cell function, with AMPs seldom measured.[14,16,35] Cryptosporidiosis and other intestinal protozoa represent an intermediate category: cathelicidins and α/β-defensins are clearly involved and can be strongly antiparasitic, but the contribution of vitamin D/VDR to these AMP responses has been inferred rather than directly tested.[65,68-70]

Clinically, the available human data linking vitamin D to protozoan parasitic diseases are generally weak and heterogeneous. Aside from a few small studies in cutaneous and canine leishmaniasis, most investigations are cross-sectional, have limited sample sizes, and do not adequately control for confounding variables such as nutritional status, co-infections, or concomitant therapies. In the context of malaria and toxoplasmosis, observational cohorts and experimental models have produced divergent findings, with reports of both beneficial and potentially harmful effects of vitamin D or vitamin D deficiency on infection and pathology.[110,112] Collectively, these inconsistencies indicate that the causal impact of vitamin D status or supplementation on clinical outcomes in protozoan infections remains uncertain and should be considered hypothesis-generating rather than definitive.

Several overarching themes emerge from the current body of evidence. First, species differences are significant (summarised in Section 4.4). The primate-specific VDRE in *CAMP* indicates that rodent models, which lack vitamin D-inducible cathelicidin, likely underestimate the relevance of this axis in human parasitic disease.[19,20,23] Second, the effects of vitamin D are highly context-dependent, influenced by macrophage polarization state, tissue niche (such as skin, gut, or systemic environments), and the composition of the microbiota, which is itself regulated by both AMPs and vitamin D/VDR signaling.[14,35,129-131] Third, vitamin D rarely exerts its effects solely through AMPs; it also modulates pattern-recognition receptors, inflammasomes, and T-cell responses. Therefore, the overall impact on parasitic infection reflects a balance between enhanced pathogen clearance and altered immunopathology.[16,25,35]

From a translational perspective, current evidence indicates that targeting the vitamin D-AMP axis holds promise, though it presents several challenges. Vitamin D is inexpensive, widely accessible, and demonstrably increases LL-37/HBD-2 levels in humans. However, the efficacy of supplementation depends on factors such as dose, timing, and baseline immune status, which influence whether supplementation enhances parasite control or primarily modulates inflammation.[14,23,25,35] Simultaneously, AMPs are being investigated as potential antiparasitic therapeutics, either alone or in combination with existing chemotherapies, due to their multi-target mechanisms and relatively low likelihood of inducing classic resistance.[68-70,132]

In summary, existing research substantiates the biological existence of a vitamin D-AMP axis and confirms its relevance in at least one protozoan infection (*Leishmania*), while also highlighting significant knowledge gaps. Future investigations should move beyond single-readout experiments and systematically integrate measurements of vitamin D metabolites, VDR activity, AMP expression, and parasite

Table 2: Graded strength of evidence for a vitamin D-AMP axis in protozoan parasitic infections.

Parasite / infection	Main site(s) of infection	Dominant data types	AMP involvement	Overall evidence grade*	Key comments (selected refs)
Leishmania spp.	Skin, liver, spleen (macrophages)	Human *in vitro* mechanistic; murine and canine *in vivo*; human observational	Direct: vitamin D/VDR → cathelicidin induction → reduced intracellular parasite burden; parasite-driven repression of CAMP	Strong	Multiple mechanistic studies in human macrophages plus in vivo and genetic data support a causal vitamin D-cathelicidin-Leishmania axis.[106-110]
Plasmodium spp.	Liver, blood	Murine *in vivo*; limited human observational	AMP role indirect / not assessed	Weak-moderate	Vitamin D analogues improve survival in mice, but effects are mainly attributed to NO and cytokine modulation; AMPs rarely measured.[111-113]
Toxoplasma gondii	Intestine, CNS, systemic	Murine *in vivo; in vitro* mechanistic; human observational	AMP role speculative (no direct measurement)	Weak	Vitamin D reduces parasite burden in some models but can worsen survival; human data show non-linear associations of 25(OH)D with serostatus; AMPs not directly studied.[114-118]
Cryptosporidium parvum	Small intestine (epithelium)	Murine *in vivo; in vitro* mechanistic	Direct AMP involvement; vitamin D link inferred	Moderate	CRAMP and human defensins are clearly antiparasitic and subverted by the parasite, but vitamin D/VDR manipulation has not yet been tested in this context.[119-123]
Giardia duodenalis	Small intestine	Murine/rat *in vivo; in vitro;* human observational	Direct AMP and mucus involvement; vitamin D role inferred (via deficiency/malabsorption)	Weak–moderate	AMP induction and degradation are well documented; chronic giardiasis associated with vitamin D deficiency, but no direct studies on vitamin D-driven AMP responses.[62,101,124-126]
Entamoeba histolytica	Colon, ileum	Murine *in vivo; in vitro* mechanistic	Direct Paneth-cell defensin activity; vitamin D role inferred (via Paneth-cell VDR)	Moderate	Cryptdin-2 is strongly amoebicidal and protective in vivo; VDR dependence of Paneth-cell defensins is established in other models, but not yet tested in amebiasis.[84,97,102,127,128]

outcomes across tissues and species. Ideally, these studies should be conducted in well-designed human cohorts and intervention trials to enable definitive conclusions regarding the therapeutic targeting of this axis in parasitic diseases.

8. Clinical and translational implications

The vitamin D-AMP axis is considered promising from a translational perspective because it targets host pathways rather than parasite molecules, which may circumvent traditional drug resistance mechanisms. Mechanistic studies in human macrophages demonstrate that vitamin D enhances cathelicidin-dependent killing of *Leishmania* spp., while parasites can suppress *CAMP* expression via CREM to evade this response.[104,106,107] Observational and genetic studies in both humans and dogs associate low 25(OH)D levels or altered VDR signalling with increased parasite burdens or more severe leishmaniasis, indicating that host vitamin D status can influence disease progression.[108,133]

8.1 Vitamin D as a host-directed adjunct

Robust clinical outcome data for parasitic diseases are limited, and existing human studies exhibit considerable heterogeneity. Most available reports are observational and rely on surrogate endpoints, such as lesion size, seropositivity, or composite clinical scores, rather than standardized measures of cure or mortality. Additionally, these studies infrequently stratify participants by baseline vitamin D status or co-morbidities. In the context of leishmaniasis, small cross-sectional studies and genetic association data indicate that low 25(OH)D levels and specific VDR polymorphisms may be associated with higher parasite loads or more severe tegumentary disease. In contrast, murine studies involving *L. amazonensis* demonstrate that dietary vitamin D_3 deficiency can paradoxically enhance resistance to infection.[106,134] Comparable uncertainty is observed in malaria and toxoplasmosis, where experimental improvements in survival have not yet resulted in consistent clinical benefits in humans. Therefore, current evidence does not support the recommendation of vitamin D supplementation as a disease-modifying therapy for parasitic infections, except for the correction of overt deficiency. Existing studies should primarily be regarded as hypothesis-generating and as justification for rigorously designed clinical trials.

In murine models of malaria, vitamin D supplementation reduces parasitaemia and mortality, suggesting that vitamin D could be evaluated as an adjunct to antimalarial chemotherapy, although the specific contributions of AMPs compared to other pathways such as nitric oxide or cytokine modulation are not fully understood.[134,135] In murine toxoplasmosis, vitamin D_3 primarily modulates inflammation rather than reducing parasite burden; however, a combination of vitamin D_3 and nitazoxanide significantly decreases brain cyst counts while minimizing immunopathology. This finding suggests that vitamin D may be most effective when used in combination therapies rather than as monotherapy.[136]

A cross-sectional study in humans with cutaneous leishmaniasis reported that patients receiving vitamin D therapy exhibited higher 25(OH)D levels, smaller lesions, and lower tissue parasite indices compared to those not receiving supplementation. Additionally, low vitamin D status combined with specific VDR ApaI genotypes was associated with increased parasite loads.[137] Canine studies further demonstrate a link between vitamin D deficiency and progression of visceral leishmaniasis, supporting the use of vitamin D repletion as an adjunct in leishmaniasis management, particularly in deficient individuals.[108] However, a murine study of L. amazonensis infection found greater resistance in vitamin D-deficient animals, highlighting that excessive or inappropriately timed vitamin D signalling may, in some cases, promote parasite survival by suppressing protective Th1 responses.[134]

Evidence from large-scale vitamin D trials in acute respiratory infections indicates that supplementation is generally safe at standard doses, with modest benefits primarily observed in individuals with significant deficiency. In vitamin-replete populations, the effects are often negligible.[138,139] By extension, in parasitic diseases, targeted correction of deficiency, rather than indiscriminate high-dose supplementation is likely to be the most effective approach, necessitating careful monitoring of calcium and renal function to prevent toxicity.

Several potential risks and limitations must be considered when evaluating vitamin D as a therapeutic adjunct. First, non-linear (U-shaped) associations between circulating 25(OH)D concentrations and immune or infection outcomes have been documented, indicating that both deficiency and excess may be harmful.[14,16,35,88] High-dose or intermittent bolus regimens elevate the risk of hypercalcaemia, nephrolithiasis, and vascular calcification, especially in individuals with pre-existing renal disease, hyperparathyroidism, or granulomatous disorders.[63,91] Second, vitamin D exerts broad immunoregulatory effects, including suppression of Th1 and Th17 responses and enhancement of regulatory T cell activity.[14] Although these effects may reduce immunopathology, they may also compromise protective cell-mediated immunity against intracellular protozoa in certain contexts, as evidenced by increased resistance to *L. (L.) amazonensis* in vitamin D_3-deficient mice.[106] Third, study design and dosing regimen are critical factors. Large, randomized trials in respiratory infections demonstrate that modest, daily or weekly doses targeted to deficient populations provide more consistent benefits than infrequent high-dose regimens, and that effects in vitamin-replete individuals are minimal or absent.[138,139] Applying these findings to parasitic diseases suggests that future trials should restrict inclusion to clearly deficient or at-risk patients, utilize physiologically appropriate replacement rather than pharmacological immune-boosting doses, and incorporate systematic safety monitoring for calcium metabolism and renal function.

8.2 AMP-based therapeutics and combinations

AMPs are also being developed as direct antiparasitic agents. Systematic and narrative reviews demonstrate that both natural and synthetic peptides derived from humans, insects, amphibians, and venomous animals exhibit potent activity against Leishmania, Trypanosoma, Plasmodium, Toxoplasma,

Giardia, and Entamoeba, often at micromolar concentrations and occasionally surpassing conventional drugs in experimental models.[54,69,70,140] The modular nature of these peptides enables sequence engineering to improve selectivity, serum stability, and bioavailability, supporting their potential as scaffolds for next-generation antiparasitic drugs.[70]

Although AMP-based therapies show significant potential, their clinical application is limited by several well-recognised challenges. Many peptides exhibit short plasma half-lives, are highly susceptible to proteolytic degradation, and demonstrate dose-dependent cytotoxicity or haemolytic activity in mammalian cells, thereby narrowing the therapeutic window.[45,68,73,99] Additionally, their broad-spectrum activity may unintentionally disrupt commensal microbiota, potentially affecting mucosal homeostasis and increasing susceptibility to secondary infections.[53,60,129] High manufacturing costs and the requirement for parenteral or local delivery methods, such as intralesional or topical administration, further hinder their implementation in low-resource, highly endemic settings.[132] These challenges highlight the necessity for iterative optimisation through rational design, chemical modification, and advanced delivery systems, including nanoparticles, liposomes, and hydrogels, as well as comprehensive preclinical toxicity testing prior to advancing AMP-based candidates to human trials.

In summary, current evidence supports the initiation of small, carefully stratified clinical trials in selected parasitic diseases, particularly cutaneous and visceral leishmaniasis. These studies should incorporate vitamin D status, VDR polymorphisms, and AMP measurements as mechanistic endpoints in addition to standard clinical outcomes.[105,108] Such trials are essential to determine the circumstances under which modulation of the vitamin D-AMP axis is beneficial and to establish dosing regimens that maximize antiparasitic efficacy while minimizing the risk of immunosuppression or metabolic toxicity. The advancement of both vitamin D-based and AMP-based interventions toward clinical application necessitates a staged translational pathway. This process should begin with *ex-vivo* and small animal studies that integrate vitamin D metabolites, VDR activity, AMP expression, and quantitative parasitological assessments. Subsequent steps include dose-finding and pharmacokinetic/pharmacodynamic studies to establish safe exposure ranges and evaluate interactions with standard antiparasitic drugs. Finally, early-phase clinical trials should be conducted in carefully selected patient groups, such as those with cutaneous or visceral leishmaniasis, stratified by baseline 25(OH)D status, VDR polymorphisms, and relevant comorbidities.[105,130,133] These trials should incorporate both clinical endpoints (cure, relapse, mortality) and mechanistic biomarkers (LL-37, defensins, cytokines, microbiota profiles) to determine which patients, if any, derive benefit from modulation of the vitamin D-AMP axis.

9. Conclusion

Over the past two decades, evidence has established that vitamin D serves as a central regulator of key antimicrobial peptides, particularly LL-37/cathelicidin and selected defensins, in human immune and epithelial cells. The vitamin D-AMP axis is well characterized at the transcriptional and signalling levels; however, its precise role in host defence against protozoan parasites remains to be fully elucidated. The strength of evidence regarding the vitamin D-AMP axis varies across different parasitic infections. In *Leishmania* infection, vitamin D-induced cathelicidin contributes to macrophage-mediated parasite control and is targeted by parasite evasion strategies. In malaria, toxoplasmosis, and intestinal protozoan diseases, associations between vitamin D status and clinical outcomes are frequently observed, and AMPs are implicated in parasite elimination and barrier protection. However, direct causal relationships between vitamin D, AMP induction, and parasitological outcomes remain limited. Species-specific differences in VDR-AMP interactions, context-dependent immunomodulation, and complex relationships with the microbiota further complicate the extrapolation of experimental findings to human disease. In summary, current evidence indicates that the vitamin D-AMP axis is a biologically plausible and, in certain contexts, demonstrably relevant component of antiparasitic immunity. To achieve clinical translation, rigorously designed mechanistic and interventional studies are required to determine the conditions under which modulation of this axis can be safely and effectively applied in the management of parasitic diseases. At present, therefore, the effect of vitamin D supplementation on real-world clinical outcomes of protozoan parasitic diseases remains ambiguous, and carefully controlled human intervention studies are needed before firm therapeutic recommendations can be made. Any effort to translate the vitamin D-AMP axis into therapy should proceed cautiously, with close attention to dosing, safety, and patient selection. Such approaches should be tested in rigorously designed, mechanism-informed clinical trials rather than through empirical supplementation or peptide use in unselected populations.

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Conflict of Interest

There is no conflict of interest.

Supporting Information

Not applicable.

CRediT Statement

Nuraly S. Akimbekov: Data curation, Formal analysis, Investigation, Resource management, Software development, and Drafting - Original manuscript. **Svetlana K. Sakhanova:** Funding acquisition, Investigation, Methodology development, Supervision and Manuscript - Review and editing. **Kuanysh T. Tastambek:** Conceptualization, Formal analysis, Funding acquisition, Investigation, Drafting - Original manuscript and Visualization. **Moldir Turaliyeva:** Investigation, Project administration and Visualization. **Dinara K. Sherelkhan:** Formal analysis, Conceptualization and Validation.

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