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CLONING AND PLANT-EXPRESSION DESIGN STRATEGIES FOR HUMAN ANTIMICROBIAL PEPTIDES: LL-37 AND DERMCIDIN AS CASE STUDIES

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Abstract *The emergence of antimicrobial resistance (AMR) has added to the search for alternatives to antibiotics. Antimicrobial peptide (AMP) is an attractive antimicrobial agent due to its combination of broad antimicrobial effects with other qualities of biomodulation of immune function and antimicrobial control of biofilms. The present review explores the comparison of the use of plant-based recombinant expression as an alternative to the use of human AMPs in bioethics, using the example of LL-37 and Dermcidin. LL-37 is a Cationic, amphipathic host-defense peptide with membrane-active, antibiofilm, antiviral, and immunomodulatory functions, whereas the peptides that result during fermentation by Dermcidin are typified by DCD-1L, which is an anionic, Dcd-derived secretory peptide. Investigating pCAMBIA2301 as a representative binary-vector construct, the review highlights peptide-specific construct planning, codon optimization, regulatory context, targeting, stabilization, and recovery. The general thesis is that the production of these peptides by plants necessitates that peptide biology be integrated with expression-system engineering instead of simply inserting a peptide-coding sequence into a vector.*

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Introduction

Antimicrobial resistance has become one of the most serious threats to global health because it reduces the effectiveness of current anti-infective drugs and makes common infections increasingly difficult to treat. The World Health Organization (WHO) defines antimicrobial resistance as the process by which bacteria, viruses, fungi, and parasites no longer respond to antimicrobial medicines, thereby increasing the risk of disease spread, severe illness, disability, and death. WHO further notes that misuse and overuse of antimicrobials in humans, animals, and plants accelerate this process, making searching for alternative antimicrobial strategies increasingly urgent (Patra et al., 2025; World Health Organization (WHO, 2023).

Among the alternative approaches currently being explored, antimicrobial peptides (AMPs) have received sustained attention because they combine broad antimicrobial activity with mechanisms that often differ from those of conventional antibiotics. AMPs are short bioactive molecules found across diverse forms of life, including mammals, insects, plants, and microorganisms, where they contribute to innate defense against invading pathogens. In addition to direct antimicrobial action, many AMPs participate in immunomodulation, inflammatory regulation, wound repair, and biofilm control, which has led to their growing recognition as multifunctional host-defense molecules rather than simple peptide antibiotics (Drayton et al., 2021; Talapko et al., 2022). Despite this promise, the practical application of AMPs remains constrained by substantial production-related challenges. Their short size, strong bioactivity, membrane-active properties, susceptibility to proteolytic degradation, and possible cytotoxicity can make them difficult to produce efficiently in conventional recombinant systems. Chemical synthesis offers sequence precision but becomes costly when larger quantities are required, while microbial hosts may suffer from toxicity, low accumulation, or peptide degradation. As a result, the central challenge is no longer only identifying biologically active peptides, but also developing production systems capable of expressing them in a stable, recoverable, and functionally useful form (Kordi et al., 2024; Shanmugaraj et al., 2021).

Within this broader production problem, plant-based recombinant expression systems have emerged as

especially promising. Plant molecular farming has developed into a major branch of biopharmaceutical engineering, with plants increasingly used as hosts for recombinant proteins, vaccines, enzymes, and other bioactive molecules. Recent reviews highlight the advantages of plant systems in terms of scalability, relatively low production cost, reduced concerns related to endotoxin contamination, and the growing sophistication of transient-expression and vector-engineering technologies. For antimicrobial peptides, plant systems are particularly attractive because they may avoid some of the toxicity and recovery limitations encountered in microbial hosts while offering flexible routes for transient screening and stable transformation (Eidenberger et al., 2023; Shanmugaraj et al., 2021).

The present review focuses on two human antimicrobial peptides, LL-37 and Dermcidin, as informative case studies for plant-based expression design. LL-37 is the only human cathelicidin-derived antimicrobial peptide and is widely regarded as a multifunctional host-defense peptide with antibacterial, antibiofilm, antiviral, and immunomodulatory activities. By contrast, Dermcidin is a sweat-gland-derived peptide precursor whose processed derivatives, especially DCD-1L, form a mechanistically distinct AMP system associated with anionic activity, membrane interaction, oligomerization, and ion-channel-like pore formation. These peptides therefore provide two biologically relevant but clearly contrasting human AMP models (Paulmann et al., 2012; Schittek et al., 2001; Voronko et al., 2025; Zeth & Sancho-Vaello, 2017). This contrast is especially useful for a design-oriented review because the biological differences between LL-37 and Dermcidin imply that they may not respond equally to the same recombinant-expression strategy. LL-37 broadly represents the classical cationic amphipathic host-defense peptide model, whereas Dermcidin-derived peptides expand this framework by demonstrating that antimicrobial activity can also arise from anionic peptides with specialized membrane-associated behavior. These differences are directly relevant to construct design, targeting strategy, stabilization, and downstream recovery in recombinant systems (Paulmann et al., 2012; Voronko et al., 2025; Wu et al., 2023).

A second major theme of this review is the role of plant binary vectors in connecting peptide biology to practical expression strategy. Recombinant AMP production in plants depends not only on the biological value of the selected peptide, but also on the architecture of the expression construct. Agrobacterium tumefaciens remains a central tool in plant biotechnology because of its natural ability to transfer T-DNA into plant cells, while binary vectors provide the practical framework through which gene insertion, regulatory control, reporter logic, and plant transformation are implemented (Bevan, 1984; Hwang et al., 2017).

In this review, pCAMBIA2301 is used as a representative vector framework for discussing plant-expression design. Public vector resources describe pCAMBIA2301 as an Agrobacterium binary vector carrying kanamycin-resistance genes and a functional gusA reporter system, making it a practical model for discussing how plant-compatible vector features intersect with peptide-specific cloning requirements. The value of pCAMBIA2301 in this context lies not simply in its use as a plasmid backbone but in its ability to illustrate how insert design, reporter replacement, regulatory context, and binary-vector architecture shape downstream expression outcomes for peptides such as LL-37 and Dermcidin (Abcam, n.d.; SnapGene, n.d.).

Although several reviews already exist on AMP biology, LL-37 biology, plant molecular farming, and plant recombinant expression more broadly, fewer studies have synthesized these topics through the narrower lens of cloning and plant-expression design for specific human antimicrobial peptides. The literature is especially rich in general discussions of antimicrobial activity and plant-expression platforms, but remains less integrated at the point where peptide biology, construct engineering, binary-vector planning, and plant-host logic intersect. This gap is particularly relevant for human peptides such as LL-37 and Dermcidin, whose successful expression in plants is likely to depend on peptide-specific sequence design, localization strategy, and recovery-oriented construct planning rather than generic vector insertion alone (Eidenberger et al., 2023; Shanmugaraj et al., 2021).

Accordingly, this review examines how peptide biology, plant molecular farming, and binary-vector architecture intersect in the design of recombinant constructs for LL-37 and Dermcidin. Particular emphasis is placed on the mechanism of action, sequence design, codon optimization, regulatory context, subcellular targeting, peptide stabilization, and recovery strategy, with pCAMBIA2301 used as a practical case-study vector. The central argument of this review is that successful plant-based expression of LL-37 and Dermcidin should be approached not merely as a peptide-selection problem, but as a rational construct-design problem in which peptide properties and expression-system engineering are deliberately aligned

Antimicrobial Peptides as Alternatives to Conventional Antibiotics

The increased resistance to antibiotics has heightened the need to find anti-infective agents whose mechanism of action is distinctly different from that of the rest of the conventional drugs. Since the core AMR issue has already been presented, this section is devoted to the reasons why AMPs should be considered one of the most powerful alternative strategies to develop antibacterials (Patra et al., 2025; WHO, 2023).

Modern medicine has been transformed by conventional antibiotics, which have the potential to destroy critical microbial processes like cell wall synthesis, protein synthesis, nucleic acid replication, and intermediary metabolism. Nevertheless, their widespread and in many cases inappropriate usage has facilitated the occurrence and propagation of resistant organisms, thus undermining the long-term efficacy of many well-established classes of drugs. The more widespread the resistance, the smaller the therapeutic lifespan of traditional antibiotics is becoming, and there is an urgent need to identify molecules capable of operating on the basis of more extensive or less easily avoided mechanisms (Ahmed et al., 2024; Rima et al., 2021).

The general definition of antimicrobial peptides implies a group of bioactive molecules that are comparatively small in size and are produced by different organisms as natural defense mechanisms. They have been described as natural effectors whose activity targets a wide spectrum of pathogens, including bacteria, fungi, and viruses. Besides direct microbicidal action, many AMPs also have a role in host-defense regulation, inflammatory modulation, and biofilm control, giving them a broader functional range than many conventional antibiotics (Drayton et al., 2021; Talapko et al., 2022).

The key benefit of AMPs is their mode of action. A large number of them interact directly with microbial membranes and may destabilize lipid bilayers, increase permeability, dissipate membrane potential, or promote leakage of intracellular contents. Others can also enter intracellular targets or modify the host immune responses following initial membrane interaction. Since their activity is often multifactorial and not limited to a single enzymatic target, AMPs are widely considered less susceptible to the classical resistance routes that defeat many traditional antibiotics (Rima et al., 2021; Talapko et al., 2022). AMPs cannot be simply substituted for the traditional antibiotics. Both therapeutic development and large-scale recombinant expression may become complicated by their low resistance to degradation, low physiological stability, potentially cytotoxic nature, delivery challenges, and high cost of production (Kordi et al., 2024; Shanmugaraj et al., 2021).

Table 1. ***Comparison of major recombinant production platforms for antimicrobial peptides***

Production platform	Main advantages	Main limitations	Relevance to AMP production
Chemical synthesis	Precise control over peptide sequence and modifications; useful for short peptides and analog development.	Expensive at a larger scale; less practical for high-volume production.	Strong for discovery, optimization, and small-scale preparation, but limited as a sole large-scale manufacturing route.
Bacterial systems	Fast growth, low cost, easy genetic manipulation, and widely used recombinant tools.	AMP toxicity to host cells, proteolytic degradation, and low soluble yield; often requires fusion tags or controlled expression.	Useful and common, but often technically difficult for membrane-active AMPs.
Yeast / fungal systems	Eukaryotic expression environment, secretion capability, and potentially reduced direct toxicity compared with bacteria.	Proteolysis, variable yield, purification challenges, and peptide-specific incompatibilities.	A flexible intermediate platform when bacterial systems are unsuitable.
Mammalian / insect systems	Can support more complex folding and processing; useful for difficult recombinant products.	Higher cost, slower scalability, and more complex culture requirements.	Scientifically useful, but often less practical for rapid or economical AMP production.
Plant systems	Scalable, relatively low cost, reduced endotoxin concerns, and compatible with transient and stable expression strategies.	Low accumulation, degradation, phytotoxicity, and downstream purification can still limit success.	Especially promising for AMPs that are difficult to express in microbial hosts; highly relevant to molecular farming.

Note. General platform comparisons are adapted from Kordi et al. (2024), while the specific rationale for plant systems is synthesized from Shanmugaraj et al. (2021), Eidenberger et al. (2023), and Nazarian-Firouzabadi et al. (2024).

LL-37 as a Human Antimicrobial Peptide Model

One of the most studied human antimicrobial peptides is commonly considered a central element of the innate immune response. It is the sole human cathelicidin, produced by proteolytic processing of the precursor protein hCAP18/CAMP, and recent reviews describe it as a multifunctional peptide with a broad antimicrobial and host-defense activity. Due to this scope of activity, the topic of LL-37 is often discussed not only as a microbial-killing antimicrobial peptide, but also as a host-defense peptide that plays roles that are not necessarily

microbial killing (Drayton et al., 2021; Voronko et al., 2025).

The structure of LL-37 is that of a 37-amino-acid cationic peptide whose name is based on its two N-terminal leucine residues. It is traditionally defined as an amphipathic α-helical peptide, and this structural organization is at the core of its biological activity since it promotes electrostatic attraction to negatively charged microbial membranes and facilitates subsequent membrane interaction. The reviews of LL-37 repeatedly highlight that its cationic and amphipathic character is the root cause of much of its antimicrobial behaviour, as well as the mechanism by which it interacts with host cells and immune pathways (Voronko et al., 2025; Zeth and Sancho-Vaello, 2017).

The antibacterial relevance of LL-37 is in its broad spectrum of activity as well as in its multifunctional mechanism of action. Through electrostatic interaction, insertion into the bacterial membrane, and the promotion of membrane permeabilization, LL-37 can bind to the negatively charged bacterial membrane, insert into the bacterial membrane, and trigger the membrane permeabilization, which may result in leakage of intracellular contents and bacterial killing. Besides direct killing, the presence of strong antibiofilm activity has also been associated with LL-37 (especially critical since biofilms tend to make bacteria less susceptible to traditional antibiotics) (Voronko et al., 2025; Wu et al., 2023).

Another reason why LL-37 is so significant is that the biological action of LL-37 is not solely based on antibacterial activity. The literature states that LL-37 is a peptide that possesses very important immunomodulatory functions, including regulation of inflammatory signaling, chemotaxis, and broader host-defense responses. Its antiviral relevance, such as the ability to interfere with the infectivity of viruses, and to alter host immune responses in manners that may enhance antiviral defense, is also noted. These expanded roles render LL-37 more than just a basic membrane-active peptide and make it more attractive as a medically relevant recombinant target (Drayton et al., 2021; Voronko et al., 2025). In the case of recombinant production, the identical characteristics that render LL-37 biologically useful also pose design challenges. Its low proteolytic stability, potentially cytotoxic nature, and cost of production imply that expression strategies need to consider stability, localization, and recovery at the very outset (Voronko et al., 2025).

Dermcidin as a Human Antimicrobial Peptide Model

Dermcidin is a unique member of the human antimicrobial peptide repertoire because, unlike a number of other host-defense peptides that are induced more often during inflammation or infection, it is constitutively expressed in eccrine sweat glands and secreted into sweat as a part of baseline skin defense. The initial discovery study has cited the presence of dermcidin in the form of an antimicrobial peptide, as a 47-amino-acid peptide that is a proteolytic processing product of dermcidin in the sweat gland. This constitutive secretion formative of the dermcidin type is specifically pertinent to the discourse of the primary epithelial line of defense (Schittek et al., 2001).

The distinguishing structural aspect of the dermcidin-derived peptides is that they are distinctively different in their structure as compared to the classical paradigm of cationic antimicrobial peptides. The most studied derivative is the DCD-1L, which was widely described as an anionic amphiphilic antimicrobial peptide that works under conditions that are similar to the conditions of human sweat. Functional and biochemical analyses demonstrate that DCD-1L exclusively binds negatively charged bacterial phospholipids, adopts an α-helical conformation in the membrane-bound form, and forms oligomeric complexes that are stabilized by Zn 2 +. These properties drive dermcidin mechanistically significant in AMP biology, and distinguish it as a more straightforward example of the more conventional cationic host-defense peptides (Paulmann et al., 2012).

Dermcidin is the antibacterial relevant amino acid, as this amino acid is associated with cutaneous innate immunity. Dermcidin also helps in the antimicrobial protection measures of the body, before the body is actually in need of antimicrobial measures. Initial discovery article and subsequent mechanistic investigations support the fact that dermcidin-derived peptides are active under the salty, physiologically relevant conditions of sweat and justify their significance as natural antimicrobial effectors in the skin (Paulmann et al., 2012; Schittek et al., 2001). Mechanistically, peptides derived by cleavage of dermcidin are of particular significance as they expand the knowledge of the mechanism of action of antimicrobial peptides. Instead of acting in the usual manner in response to some standard cationic membrane-disruption paradigm, it has been demonstrated that DCD-1L is capable of oligomerizing and of promoting ion-channel-like pore formation in bacterial membranes. This results in the depolarization of the membrane, the imbalance of the ions, and ultimately, the killing of the bacteria. The relevance of the existence of this mechanism to the design of recombinant-expression systems is significant because peptides that follow such a typical cationic AMP model (Paulmann et al., 2012; Zeth and Sancho-Vaello, 2017) may require different strategies of stabilization, localization, and expression than do the peptides that follow such a paradigm. In terms of recombinant expression, dermcidin is of value as it does not take the typical cationic AMP stereotype. Its anionic charge, physiology related to sweat, and self-assembly behavior make it a robust comparator to find out whether construct designing needs to be designed to be peptide-specific rather than generic.

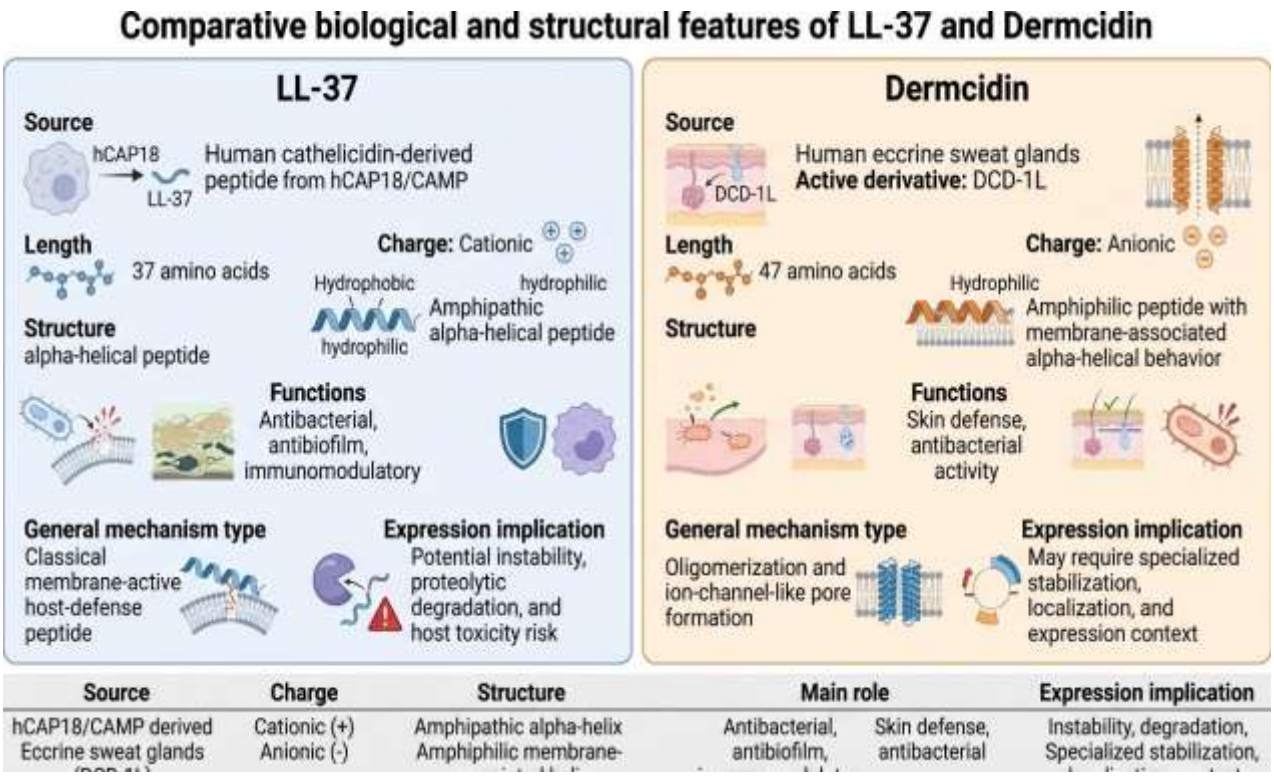

Figure 1. ***Comparative biological and structural features of LL-37 and Dermcidin***

Table 2. ***Comparative features of LL-37 and Dermcidin relevant to recombinant-expression design***

Peptide	Source	Charge and structure	Principal functions	Main mechanism	Expression implications
LL-37	Human cathelicidin-derived peptide released from hCAP18/CAMP	Cationic; amphipathic α-helical peptide	Antibacterial, antibiofilm, immunomodulatory, and antiviral relevance	Electrostatic interaction with negatively charged bacterial membranes, membrane permeabilization, leakage of intracellular contents, and antibiofilm activity	Proteolytic instability, potential cytotoxicity, and difficulty of stable, cost-effective recombinant production
Dermcidin / DCD-1L	Human eccrine sweat-gland-derived antimicrobial peptide system; DCD-1L is an active processed derivative present in sweat	Anionic; amphiphilic peptide with membrane-associated α-helical behavior and oligomerization capacity	Constitutive skin-surface defense and antibacterial activity	Membrane interaction, oligomerization, ion-channel-like pore formation, membrane depolarization, ion imbalance, and bacterial killing under sweat-like conditions	Likely peptide-specific requirements for stabilization, localization, and expression context due to unusual charge properties and self-assembly behavior

Note. The LL-37 entries are synthesized from Voronko et al. (2025) and Wu et al. (2023); the Dermcidin entries are synthesized from Schittek et al. (2001), Paulmann et al. (2012), and Zeth and Sancho-Vaello (2017)

Comparative Significance of LL-37 and Dermcidin

The two peptide antimicrobials, LL-37 and Dermcidin, are useful paired case studies since both are human antimicrobial peptides, but they differ sharply in charge, physiological context, membrane behavior, and probably requirements of recombinant expression. One of them is LL-37, the classical cationic amphipathic host-defense model, and the other one is Dermcidin/DCD-1L, an anionic, sweat-associated system, active under sweat-like conditions (Paulmann et al., 2012; Schittek et al., 2001; Voronko et al., 2025). Their similarity as human innate-defense peptides ensures that the review is translationally focused, and their mechanistic differences make the comparison design-relevant. It is possible to review common AMP production issues using a review based on these two peptides, without necessarily assuming that every AMP will need the same architecture to be expressed (Paulmann et al., 2012; Voronko et al., 2025). This is of importance since having an expression system that maintains anionic, oligomeric, membrane-associated behavior may be a requirement of LL-37, and possibly not of Dermcidin. The comparison then seizes the terrain to discuss more later peptide-specific cloning, targeting, stabilization, and recovery of peptides (Paulmann et al., 2012; Schittek et al., 2001; Voronko et al., 2025).

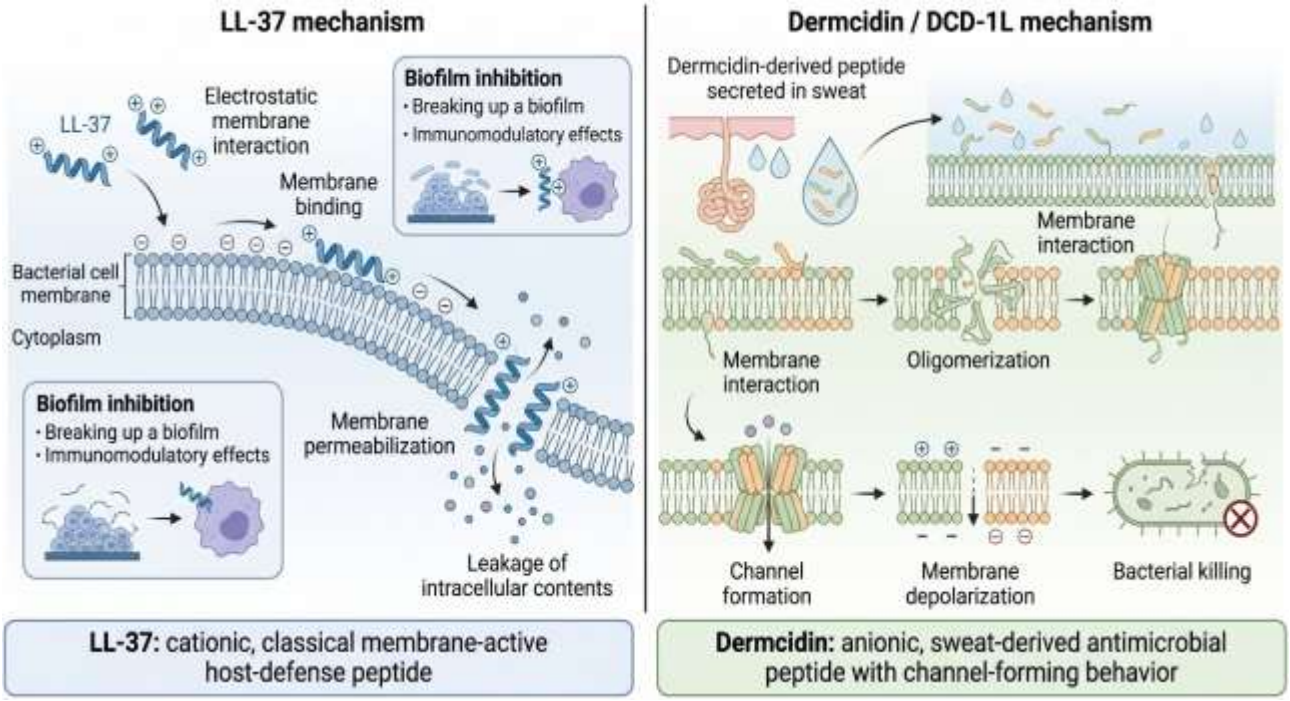

Figure 2. ***Comparative antibacterial mechanisms of LL-37 and Dermcidin***

Recombinant Production Platforms for Antimicrobial Peptides

The therapeutic and biotechnological potential of antimicrobial peptides has brought the efficient production of antimicrobial peptides into the central focus of interest in the area. Even though most AMPs exhibit broad-spectrum antimicrobial actions and appealing host-defense capabilities, their translation into useful products hinges on their ability to be prepared in usable amounts in a pure, high-quality form and at a stable, sufficiently high level. Empirical reviews on the manufacturing of AMP highlight the realization of the main challenge, which is not only finding bioactive peptides produced in vivo, but also establishing production platforms that can balance yield, bioactivity, host compatibility, and downstream recovery (Kordi et al., 2024; Nazarian-Firouzabadi et al., 2024).

Chemical synthesis is one of the oldest and most straightforward pathways in the production of AMP. Peptide synthesis in solid phase remains popular due to the ability to control precisely sequence composition, substitution of residues and alterations in structure, which makes it particularly useful in synthesizing short peptides and in the development of analogs. With large amounts of peptides that are needed or repeated optimization cycles that must be done, chemical synthesis becomes more and more costly and unfeasible. In such a way, chemical synthesis can be useful in discoveries and limited-scale preparation, but cannot always be adequate as the sole approach to scalable production of AMPs (Kordi et al., 2024). The bacterial expression system, in particular, Escherichia coli, is still popular due to its rapidity, relative inexpensiveness, and availability of well-established molecular tools. Their advantages are their rapid growth, easy genetic manipulation, and their capability to produce recombinant products at relatively low cost. But the general response to AMP production in bacteria is typically problematic; either the peptides themselves may be toxic to the microbial host, or the peptide may have an adverse effect on membrane integrity, or the peptide may be rapidly degraded. This is why the production of the bacterial adequate to achieve a specific phenotype by convention requires protective mechanisms, such as

fusion tags, inclusion-body formation, secretion systems, or tightly controlled conditions of production (Kordi et al., 2024).

Yeasts and other fungal systems interpose between the simplistic activities of bacteria and the more complex expression milieu in eukaryotes. Reviews of heterologous AMP production report that yeast can be able to offer benefits, including secretory capability, a eukaryotic folding environment, and reduced toxicity relative to bacterial hosts in some instances. Meanwhile, these systems, too, do not always work best, as yield, proteolysis, product recovery, and, depending on the peptides in question, peptide-specific incompatibilities, can all still serve as a limiting factor. What is valuable about them is that they can be used to optimize peptides specific to various bacteria requiring optimization, unlike bacteria, yet they still require optimization to be performed (Kordi et al., 2024).

More complex folding or processing environments are also applicable when peptides need a more complex environment. These hosts are able to facilitate advanced post-translational processes and can, in some instances, enhance functional restoration of challenging peptides. Nevertheless, their broader application is often constrained by a higher cost, slower scaling, and more complex culture support requirements, and overall increased burden of the higher-end biomanufacturing platforms. In the case of AMP production, they can be scientifically useful, yet they are not necessarily the most practical first choice when it comes to cost-effective manufacturing or rapid construct screening (Kordi et al., 2024).

This analogy includes plant-based systems of production as they combine scalability, lessened concerns about endotoxins, and flexible, sustainable, transient, or stable expression strategies. The remaining limitations and strengths of each of them, in particular, AMPs, are discussed in more detail in the following section (Eidenberger et al., 2023; Nazarian-Firouzabadi et al., 2024; Shanmugaraj et al., 2021).

Plants as Expression Platforms for Human Antimicrobial Peptides

Molecular farming is increasingly using plants as hosts due to their ability to support scalable and flexible production of recombinants. In the case of antimicrobial peptides, this platform is desirable as it could potentially reduce certain microbial-host toxicity issues without necessarily reducing the overall ability to control the construct-level expression, localization, and recovery (Eidenberger et al., 2023; Shanmugaraj et al., 2021). There are two broad categories of plant expression strategies: stable and transient systems. In stable transformation, the transferred DNA integrates into the plant genome and can then be transcribed to be briefly expressed. This difference is of particular significance to recombinant AMP production as stable transformation is more appropriate to long-term expression programs and development of hereditary traits, whereas transient systems are especially valuable to test recombinant constructs or to screen small sets of constructs, and the rapid production of proteins (Hwang et al., 2017). Nicotiana benthamiana is now one of the most significant chassis in contemporary plant molecular farming. According to reviews, N. benthamiana is a key host in recombinant production, and the focus on using transient-expression vectors and elements that have a viral origin to achieve high and rapid accumulation of targets produced may involve this host. This is particularly applicable in the case of antimicrobial peptides, where rapid comparison of alternative constructs may turn out to be more valuable than immediate commitment to stable line development (Eidenberger et al., 2023).

A range of particular studies confirms the relevance of plants to the production of AMP. DeGray et al. have challenged this hypothesis by showing that a synthetic antimicrobial peptide MSI-99 could be expressed in the genome of the chloroplast of tobacco, indicating that the chloroplast organelle can serve as a high-expression organelle with respect to antimicrobial peptides. Recently, a high-yield plant-based AMP-production strategy was reported by Chaudhary et al., where peptides were secreted via the endomembrane system and recovered in the apoplast, demonstrating a direct linkage between the localization strategy and downstream recovery and production cost (Chaudhary et al., 2024; DeGray et al., 2001).

The AMP-production issues are not automatically filtered by plant systems. The major barriers, in particular, the poor match of construct design to plant physiology or subcellular localization, remain significant impediments (Shanmugaraj et al., 2021). The inference is clear in the case of LL-37 and Dermcidin, where the expression of each peptide determines success. The following part resorts to the Agrobacterium-mediated transformation and binary vectors for agricultural plants, which offer the molecular framework upon which those design choices were implemented.

Agrobacterium-Mediated Transformation and Plant Binary Vectors

The application of plants as recombinant production hosts is inextricably linked to Agrobacterium tumefaciens, which remains one of the most significant tools in plant biotechnology due to its naturally occurring ability to transfer a fragment of DNA, called T-DNA, into plant cells. Reviews call Agrobacterium-mediated transformation as a central technique used in plant engineering and note that transferred DNA may be either integrated into the plant genome to become permanently transformed or if it does not become fixed to the genome to become permanently transformed then it remains non-integrated yet still can be transcribed in transient-transformation systems (Hwang et al., 2017). The practical significance of this system of transformation

is not just the bacterium itself, but also the molecular tools that have been created around it. One of the biggest improvements came when they created the system of binary vectors, breaking apart the DNA region that needs transferring and the larger virulence machinery that is needed to transfer it. The original work by Bevan was a description of a design of a system of vectors, which relies on the trans-acting functions of the vir region of a co-resident Ti plasmid to transfer sequences framed by left and right Ti T-DNA boundary repeats into the plant nuclear genome. This design ensured that plant transformation was a whole lot more practical as it allowed the researchers to manipulate a smaller, convenient plasmid backbone and rely on Agrobacterium to provide the transfer machinery in trans (Bevan, 1984). Later sources started using binary vectors as the common instrument in the transformation of higher plants. Surveys of T-DNA binary systems highlight the fact that the typical binary vector would include the T-DNA borders, multiple-cloning region, and Escherichia coli and Agrobacterium replication functions and selectable marker genes. This can be done in practical terms, where a gene of interest is inserted into a manageable shuttle vector, which can be subsequently propagated in bacterial hosts and then transferred into plant cells by Agrobacterium. This modular design is especially applicable to recombinant-expression research as it enables the integration of both the construction of vectors and their incorporation into bacterial cells and the delivery of the construct into a plant, and downstream selection into a single workflow (Bevan, 1984; Hwang et al., 2017).

In the case of recombinant antimicrobial peptides, binary-vector architecture is particularly critical since these peptides typically are encoded by small inserts whose performance is highly sensitive to their relative position within the expression cassette. Under these circumstances, promoter-context, reading-frame integrity, placement of the translational start and stop codons, and compatibility with reporter or fusion arrangements have become critical design issues instead of minor, technical concerns. Agrobacterium-mediated delivery is not, therefore, a transport step, but rather a subset in a larger engineering framework in which the archiving is directly influenced by the vector architecture, which determines the format of how the transgene will be tested, expressed, and ultimately interpreted in the plant tissues. It sets the scene of the case study of pCAMBIA2301, which is used below as a representative binary-vector framework for discussing how insert design, regulatory architecture, selection, and screening can be coordinated with respect to short human AMP constructs.

pCAMBIA2301 as a Case-Study Vector

One particularly useful case-study backbone to design recombinant constructs, attributed to its usefulness, is pCAMBIA2301, a binary vector of Agrobacterium which carries both kanamycin-resistance genes and a working GUS/gusA reporter system. These characteristics contribute to the relevance of this tool not only on the basis of the analysis of the final transformation reproductive phenotype but also towards the analysis of transformative reproductive phenotypes in the initial phase of differentiation and development (Abcam, n.d.; SnapGene, n.d.). The practical benefit of pCAMBIA2301 is that it has combined the convenience of bacterial manipulations with the compatibility of plant transformation. The description of the product documents indicates that the vector has a high copy number in E. coli to yield high DNA amounts, a pVS1 replicon to maintain stability in Agrobacterium, a relatively small size of the vector to facilitate canary leaf style and ligation cloning techniques on the portion, and restriction sites to provide modular plasmid modification with a polylinker to allow easy insertion of genes of interest. The properties are significant in construct-development workflows due to the fact that they facilitate routinely performed cloning, plasmid growth, and transfer to plant transformation systems without altering the underlying architecture (Abcam, n.d.). The second significant strength of pCAMBIA2301 is its selection and reporter architecture. Public records indicate the presence of bacterial and plant selection genes with kanamycin and an active gusA reporter construct, sensitive analysis in regenerated plants in the vector. As reported in the same documentation, the genes in the pCAMBIA vectors that drive the plant selection genes are driven by a double-enhancer version of the CaMV 35S promoter and terminated by the CaMV 35S polyA signal. This framework renders pCAMBIA2301 particularly valuable when it comes to discussing how a peptide-expression cassette can be inserted into a plant-compatible transformation system and still be able to screen downstream (Abcam, n.d.).

To review the design of antimicrobial peptide constructs, a major focus of the design of pCAMBIA2301 is its modularity. According to the corresponding product guidelines, reporter elements like gusA could be substituted by a gene of interest, and guidance on approaches to adapt pCAMBIA2301 as a practical insertion backbone to transform plants depends on the goals of the experiment. This is of particular essence to LL-37 and Dermcidin, in that both recombinant targets are short peptides and the success of their downstream expression will depend on not only the insertion itself, but also the choices made regarding the integrity of reading frames, reporter replacement, translational design, and expression-cassette configuration (Abcam, n.d.; SnapGene, n.d.). pCAMBIA2301 in this review, therefore, is illustrative as opposed to exclusive. It offers a hands-on binary-vector model to discuss how peptide-coding sequences, reporter logic, selection, and the ability to deliver via Agrobacterium can be

coordinated in the design of plant AMP constructs (Abcam, n.d.; Hwang et al., 2017).

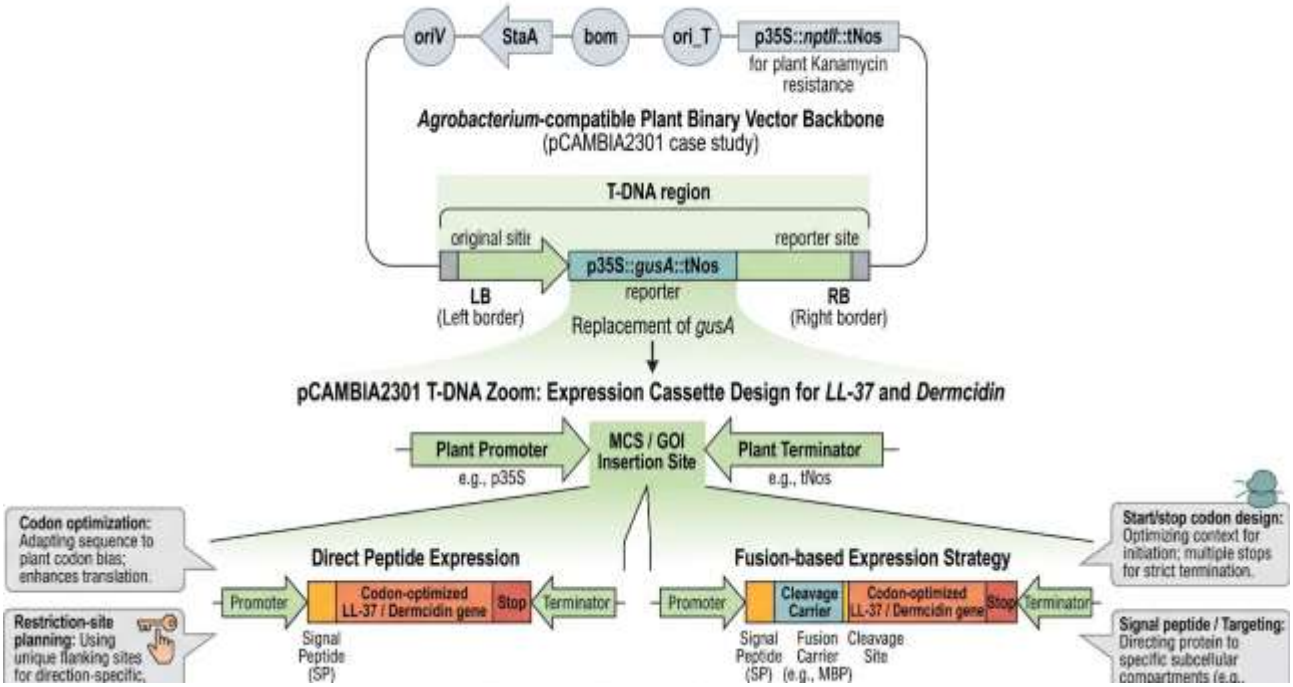

Figure 3. ***Schematic representation of pCAMBIA2301-based construct design for LL-37 and Dermcidin expression***

Core Cloning and Construct-Design Considerations for LL-37 and Dermcidin

In the case of LL-37 and that of Dermcidin, construct architecture is as critical in establishing successful plant expression as either of the peptides. The design of the coding sequence, regulatory elements, subcellular localization, stabilization, and recovery strategy all have an impact on whether a biologically promising AMP becomes a recoverable recombinant product (Eidenberger et al., 2023; Shanmugaraj et al., 2021). One way of designing is based on the fundamentals of the architecture of the insert. Open reading frame integrity, insertion orientation, and placement of the start-codon, logic at stop-codons, and compatibility with reporter or fusion variant become key drivers of construct performance, as opposed to minor technical concerns (Abcam, n.d.; SnapGene, n.d.). The second significant problem is the codon optimization. Though codon optimization may not necessarily result in high expression, up-to-date reviews clarify that the synonymous codon choice may have effects on translational efficiency and wider sequence-level effects that are pertinent to heterologous expression. As LL-37 and Dermcidin are synthetic, human peptides, which are destined to be expressed in a plant host, their native coding sequences might not be optimal for the plant translation machinery. It is the rational approach to cloning that must take into account codon usage and associated sequence-design variables that can enhance the probability of productive gene expression without changing the peptide product per se (Paremskaia et al., 2024).

The third fundamental would be the promoter review terminator surrounding. Promoters and terminators are no longer viewed as parts of vectors passively involved in the promotion and termination of gene expression, but as central regulatory factors of expression themselves. Brooks et al. observe that a combination of promoter and terminator not only modulates termination of transcription, but also influences 3CL-stabilization, mRNA-stability, translation-efficiency, and nuclear-to-cytoplasmic-export. In the case of LL-37 and Dermcidin, this implies that a successful attempt to express the peptide-coding sequence into plants will not only rely on a precise insertion of the sequence into the user of officially approved plasmid vectors, but also on the contextualization of the peptide-codifying sequence within an effective plant regulatory context (Brooks et al., 2023). Subcellular targeting is a fourth variable of design. Among the most evident implications of the new plant AMP-production research is that the compartment where a peptide gathers may have a powerful influence on the success of expression, compatibility with the host, and the subsequent recovery. As reported by Chaudhary et al., in a plant-based AMP-production strategy in Nicotiana benthamiana, peptides were produced by secreting them through the endomembrane system and apoplast deposition, thus simplifying downstream processing and thereby aiding in reducing the production cost. This is highly significant to the case of LL-37 and Dermcidin because both are short and highly bioactive, yet they differ substantially in membrane behavior, and they are likely to be intracellularly incompatible (Chaudhary et al., 2024).

The fifth consideration is that either the peptide needs to be expressed as a free mature peptide or as part of a fusion-based design. Repeated reviews of Plant AMP systems note that short antimicrobial peptides tend to accumulate poorly and are vulnerable to degradation. It is of particular interest to LL-37 and Dermcidin since being small in size exposes them to proteolysis, and their biological activity poses stress to the host in the event that the two accumulate without protection. A fusion strategy can enhance stability or enable purification, but may also add new stability conditions or cleavage requirements (Chaudhary et al., 2024; Shanmugaj et al., 2021).

The sixth significant consideration is related to host compatibility and toxicity involving peptide association. Traditional empirical evidence on the role of high bioactivity AMPs always demonstrates that high bioactive peptidomics can disrupt host physiology when it is expressed in an inappropriate format or compartment. This is of particular concern to LL-37, as this is a very strongly cationic and membrane-active peptide; this is also a significant concern to Dermcidin. Dermcidin is also an extremely strongly cationic and membrane-active peptide, but it is also of significant concern. The practical implication is that effective cloning should not simply aim to maximize transcription, but to achieve some form of expression that will be tolerable biologically, sufficiently stable, and compatible with the host intracellular environment (Shanmugaraj et al., 2021).

A seventh consideration is downstream processing/recovery, which must be considered a part of construct design and not a manufacturing issue. Recent work in the expression of plant-based AMPs has explicitly demonstrated the correlation between expression architecture and cost of purification and production feasibility, indicating that secretion-based approaches and apoplastic sequestration can simplify recovery of difficult peptides. As important as this point is when we consider a plant-expression review with a focus on LL-37 and Dermcidin, in this case, should recovery be ignored in the design of the construct that will be expressed? Then a construct that is capable of expression may nonetheless prove impractical. Therefore, the reasoning of expression, localization, and purification must be incorporated throughout the initial phases of planning the vectors (Chaudhary et al., 2024; Eidenberger et al., 2023).

Lastly, the LL-37 and Dermcidin can demand varied design solutions using the identical backbone of the vectors. The successful expression of human LL-37 in barley over six generations is a piece of evidence that plant expression of a human AMP can be successful, but also demonstrates the need to design a sequence, host environment, targeting, and recovery to meet the desires of an individual peptide (Mirzaee et al., 2021; Shanmugaraj et al., 2021).

Table 3. ***Key construct-design considerations for plant expression of LL-37 and Dermcidin***

Design factor	Why it matters	Relevance to LL-37	Relevance to Dermcidin	Expected effect on downstream expression
ORF integrity and start/stop codons	Short peptide inserts are highly sensitive to frame errors, truncation, or incorrect assembly.	Critical because LL-37 is only 37 aa, and small sequence errors can abolish peptide activity.	Critical because dermcidin-derived constructs also encode a short active peptide region and require precise sequence preservation.	Correct peptide translation and functional product formation.
Restriction-site planning/insertion logic	Internal restriction sites, incompatible ends, or poor insertion planning can compromise construct assembly.	Important because LL-37 inserts are short and cloning errors are harder to detect functionally.	Equally important because dermcidin constructs may require precise replacement or fusion design.	Improves cloning efficiency and construct stability.
Codon optimization	Synonymous codon choice can influence translational performance and other sequence-level expression properties.	Relevant because LL-37 is human-derived and intended for plant expression.	Relevant because dermcidin is also human-derived and may require plant-compatible sequence engineering.	May improve translational efficiency and expression consistency.
Promoter–terminator context	Promoters and terminators influence transcript abundance, stability, processing, and translation.	Important if the expression must be strong but biologically tolerable for a	Important if expression must support peptide accumulation without	Affects expression level and transcript quality.

		membrane-active peptide.	disrupting functional behavior.	
Fusion strategy vs free-peptide expression	Short AMPs often accumulate poorly or degrade rapidly unless stabilized by a larger fusion context.	LL-37 may benefit from protection against degradation and host-associated stress.	Dermcidin may require stabilization depending on how the active peptide is expressed and recovered.	Can improve peptide stability, accumulation, and recovery.
Signal peptide/targeting sequence	Subcellular localization influences host compatibility, peptide stability, and purification feasibility.	LL-37 may require controlled localization because of its cationic membrane-active nature.	Dermcidin may require a different targeting strategy because of its distinct physicochemical and membrane-associated behavior.	Can improve stability, reduce host burden, and simplify recovery.
Host compatibility / peptide-associated stress	Highly bioactive peptides can burden or damage the expression host if produced in an unsuitable format or compartment.	Especially relevant because LL-37 is strongly cationic and membrane-active.	Relevant because dermcidin is mechanistically unusual and may impose a different but still significant burden on the host.	Affects expression success, plant fitness, and recoverable yield.
Proteolytic stability and recovery strategy	Small peptides are often vulnerable to degradation; recovery feasibility should be considered during construct design.	LL-37 is known to face stability limitations that complicate production and purification.	Dermcidin may also require protection depending on construct format, compartment, and secretion strategy.	Determines peptide accumulation, practical usefulness, and production cost.

Note. This table synthesizes pCAMBIA2301 guidance from Abcam and SnapGene with sequence-design, regulatory, targeting, and recovery considerations discussed by Paremskaia et al. (2024), Brooks et al. (2023), Chaudhary et al. (2024), Shanmugaraj et al. (2021), and Mirzaee et al. (2021).

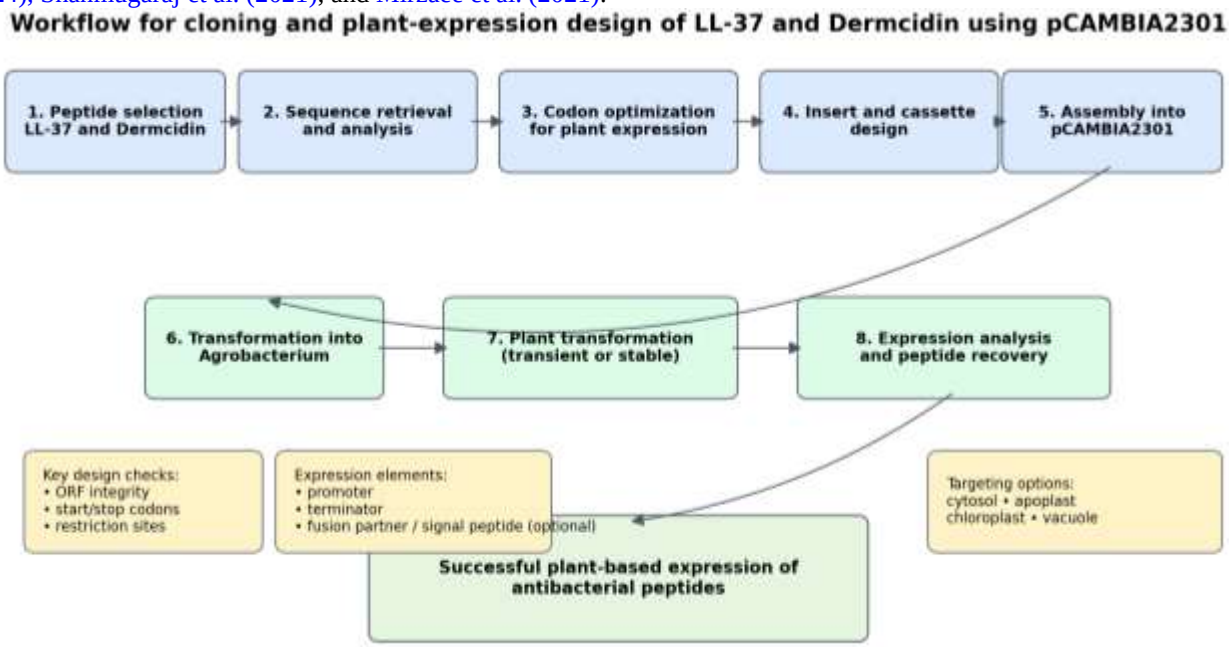

Figure 4. ***Workflow for cloning and plant-expression design of LL-37 and Dermcidin using pCAMBIA2301***

Why LL-37 and Dermcidin May Require Different Cloning Solutions

In spite of the fact that LL-37 and Dermcidin can be seen as the results of a common plant-based production strategy of AMPs, they are not to be considered as interchangeable recombinant targets. Their various charge properties, interactions with membranes, and physiological contexts influence sequence design, stabilization, localization, and host compatibility (Paulmann et al., 2012; Schittek et al.,

2001; Voronko et al., 2025). In the case of LL-37, the primary design pressure will be the cationic, amphipathic, membrane-active character of the compound. These properties allow the support of antimicrobial and antibiofilm activities, but these properties can also lead to a situation where the peptide is accumulated unprotected in sensitive compartments. Constructs of LL-37 can thus focus on stabilizing by fusion, controlled localization, or secretion-oriented recovery (Shanmugaraj et al., 2021; Voronko et al., 2025; Wu et al., 2023).

The Dermcidin is a different problem since DCD-1L is an anionic amphiphilic peptide related to oligomerization and ion-channel-like pore formation. It can even be designed, based on its construct design, not to rely as much on cationic peptide logic as it does on maintaining the structural and physicochemical conditions required to maintain self-assembly and membrane-associated functionality (Paulmann et al., 2012; Schittek et al., 2001). Practically, the (alleged) common pCAMBIA2301 backbone would not bone out peptide-specific choices. It might be that an increased level of protection of host stress and degradation is required of the LL-37, and a lower level of protection toward their unusual charge and assembly properties is required of the Dermcidin. The emphasis of codon-optimization, which focuses on signals, choice of fusion-partners, strategy of secretion, and the recovery route may thus differ in the two peptides (Chaudhary et al., 2024; Shanmugaraj et al., 2021). The fact that a common plant-expression platform is not a common best solution to cloning. The practical issue is to match the vector architecture, regulatory context, localization, stabilization, and recovery to the complex, species-specific example of a biology behavior.

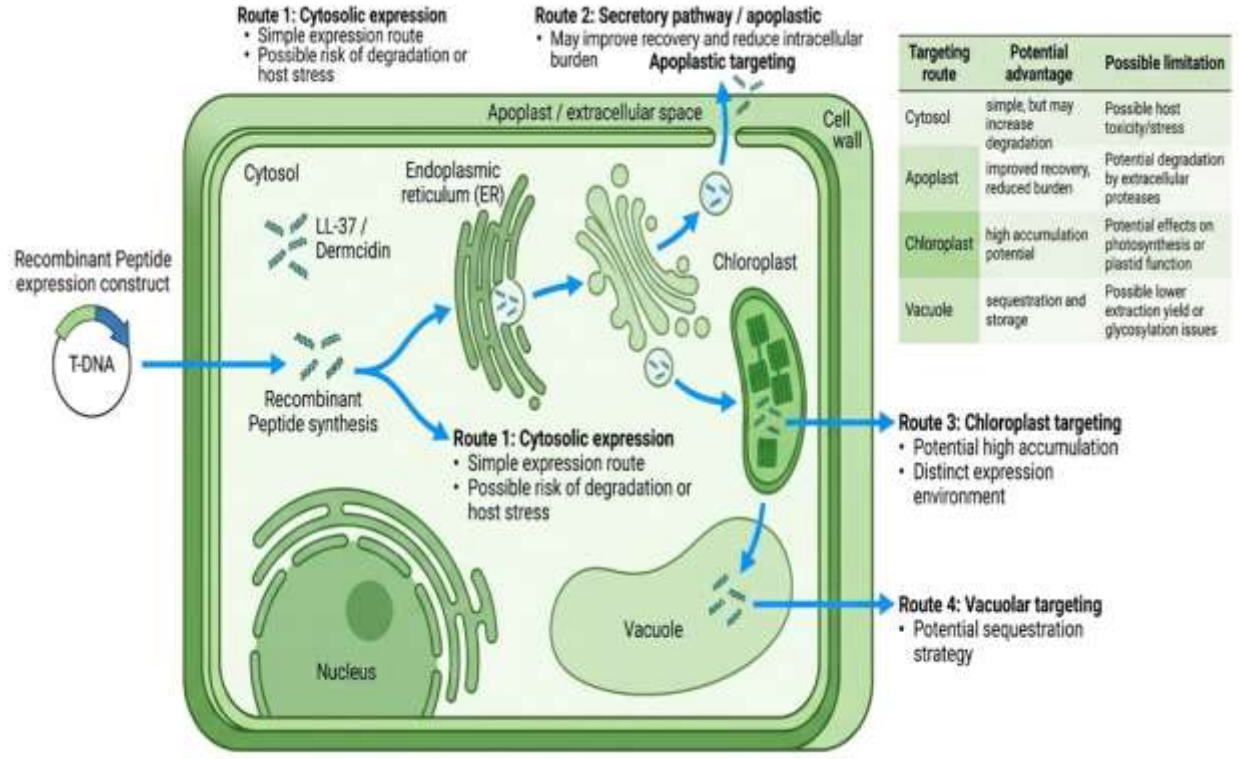

Figure 5. ***Potential subcellular targeting strategies for plant-based expression of LL-37 and Dermcidin.***

Current Gaps in the Literature

The existing literature is well covered concerning three adjacent areas, and is less so in terms of synthesis at the intersection. First, there are general reviews on the expression and production of antimicrobial peptides in plants, which summarize molecular-farming strategies, stable and transient expression strategies, and the overall promise of plants as hosts of AMP production. Second, the recent peptide-oriented reviews are devoted to the biological functions of the peptide together with its therapeutic potential and strategies of its modifications. Third, general surveys of plant-based biopharmaceutical engineering are found that comment less on the use of plants and more on the use of different vectors (including plasmid vectors, polymerase chain reaction vectors, and cassava vectors). Collectively, these sections of the literature present a concrete foundation, though they do not yet fully clarify the specific design questions that had to be addressed by the human AMP expression of plant binary vectors using binary vectors (Eidenberger et al., 2023; Shanmugin et al., 2021; Voronko et al., 2025).

The first significant gap is that there is a limited supply of reviews that specifically concentrate on human antimicrobial peptides as targets of plant expression. AMP reviews by the plant AMP is an effective albeit broad survey of plant production activities across a wide range of peptide sources and uses, rather than focusing on human peptides, which

have a specific translational value, such as LL-37 and Dermcidin. Similarly, the reviews of the LL-37 recombinant construct design are abundant in biological and therapeutic content, but generally do not focus primarily on the design of plant-based recombinant construct designs, and Dermcidin is typically not the primary topic of structural or mechanistic studies, or the focus of papers on the design of plant-based recombinant construct designs (Paulmann et al., 2012; Shanmugaraj et al., 2021; Voronko et al., 2025). The second gap would be that no literature treats LL-37 and Dermcidin as a purposeful comparison of designs. The new reviews are well characterized with the presence of LL-37, whereas a dedicated synthesis that uses these two human peptides concurrently as contrasting case studies in the context of plant-expression strategy is not provided in the available literature. This is important because there is a charge difference between LL-37 and Dermcidin, which cannot be attributed to an individual broken trial, nor can it be blamed on a handful of mammalian cells. A third gap involves the relative dearth of synthesis on the construct-design logic of plant AMP expression. In recent plant-expression literature, it is evident that success is determined by the design of vectors and hosts, regulatory architecture, transient-expression systems, and downstream-processing considerations. Most available articles, however, do not present them in a specific format covering the scope of short, challenging, antimicrobial peptides produced by humans, but instead they discuss them at the general molecular-farming level or in the context of each of the individual production studies. Specifically, existing reviews have yet to present a focused discussion on how any of the sequence engineering, localization strategy, stabilization, and recovery planning approaches should be implemented at the cloning stage in the case of peptides such as LL-37 and Dermcidin (Eidenberger et al., 2023; Shanmugaraj et al., 2021).

The fourth gap is that the review has limited attention to the binary-vector-specific planning of AMP expression. With general plant-transformation literature and available public vector resources, vectors like pCAMBIA2301 provide selectable markers, reporter logic, and modular cloning capabilities, which can suitably be applied in plant engineering, but at a relatively low level of literature. The required elements are present, yet these are not frequently incorporated into such a one-point design analysis. These gaps warrant a review that is no longer bound to general AMP background or even general plant-expression system or binary-vector construct planning, but rather rebuilds the whole biological framework within the framework of molecular farming.

Future Directions

Further upkeeping of plant-based synthesis of LL-37 and Dermcidin should concentrate on experimentally testing design choices as opposed to replicating general assertions of AMP promise. Plant systems can be optimized in a coordinated manner, and coordinated optimization of hosts, vectors, regulatory elements, targeting routes, and recovery strategies can be considered a most useful next step (Eidenberger et al., 2023; Shanmugaraj et al., 2021). A single urgent task is the systematic analysis of the construct architectures of LL-37 and Dermcidin. Recent research and reviews have strongly supported the significance of those variables like codon optimization, promoter-terminator combinations, fusion-based stabilization, and the use of variables on an insert level basis, but these characteristics are still often manipulated individually rather than evaluated in an integrated and comparative manner. The subsequent work, therefore, should compare alternative coding-sequence designs, regulatory designs, and expression forms in a systematic way and identify the combinations that have the best balance between peptide accumulation, host compatibility, and biological activity (Brooks et al., 2023; Paremskaia et al., 2024).

A second significant trend is the fact that transient plant-expression systems are now more frequently utilized as high-throughput screening systems. In the literature of molecular farming using plants, transient expression, especially in Nicotiana benthamiana, is highlighted as one of the most potent techniques of rapid prototyping of recombinant-protein expression. In the case of LL-37 and Dermcidin, its approach to future research is to use transient systems not only to produce them, but also to conduct comparative tests of localization strategies, fusion partners, promoter|terminator combinations, and other construct architectures before stable transformation is pursued. This would result in a more efficient and rational iterative development of plant-based AMPs (Eidenberger et al., 2023; Hwang et al., 2017).

The third notable direction is the subcellular targeting and recovery-focused design. Recent AMP production work on plants demonstrates that the endomembrane system secretion and apoplastic sequestration can enhance recovery and lessen the complexity of downstream processing. This will be particularly applicable to LL-37 and Dermcidin since both are short and bioactive, although they differ considerably in physicochemical behaviour and possible effects on the host. Future research must thus compare compartment-specific strategies of cytosolic, secretory, chloroplast, and other compartments in a peptide-specific manner, and with the express consideration of both purification feasibility and biological compatibility (Chaudhary et al., 2024).

The fourth priority is the improvement of the host-vector systems involving the expression of peptides. Still of interest within the broader plant-biomanufacturing literature has been the emphasis on improving hosts, having more specific regulatory elements, and even the improvement of the

architecture of vectors in terms of how well they can produce recombinant proteins. In system set-ups powered by either pCAMBIA2301 or a corresponding binary-vector of plants, this can mean that future success would depend on a combination of classical binary-vector frameworks or more advanced regulatory modules, or improved peptide-targeting choices, or host backgrounds maximized to allow the peptide to remain stable and accumulate in the body (Brooks et al., 2023; Eidenberger et al., 2023). The work of the future should also relate the expression testing to the application in the downstream. The following question is not just whether or not plant expression is possible, but whether the peptides can be produced reliably, safely, and recoverably as suitable material to be used in antimicrobial research and application (Chaudhary et al., 2024; Shanmugaraj et al., 2021).

Conclusion

This review has discussed the interface between the antimicrobial peptide biology and plant-based recombinant production. AMPs keep their attractiveness due to their robust activity and varied functionalities, yet their usefulness hinges on the execution, stabilization, and recovery solutions that are capable of handling small, bioactive peptides. The case studies of LL-37 and Dermcidin are of particular interest due to their status as both human AMPs (but not identical). LL-37 is a cationic, membrane-bound system of host-defense that is an oligomeric, ion-channel-like system, whereas Dermcidin-derived peptides are an oligomeric and ion-channel-like, anionic system, which is sweat-associated. Plant-based expression is to be considered as a construct-based design challenge. This has to be incorporated at the outset, especially in the short and highly bioactive peptides. The pCAMBIA2301 framework comes in handy in this regard as it is a representative binary-vector framework since it connects the insert design, selection, reporter logic, and Agrobacterium-mediated delivery. The larger point is not a vector-Specific production of human AMPs by plants should be intentionally aligned with the engineering of the expression system. The shared plant host or binary vector, therefore, would not imply shared optimum expression program; peptide-specific construct engineering needs to be viewed as the cornerstone to downstream success.

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Statements and Declarations

Data Availability statement

All relevant data are within the manuscript file.

Author's Contribution Statement

All authors contributed to the conception, literature review, manuscript drafting, critical revision, and final approval of the review article. MFR and SA contributed equally to the preparation of the manuscript. All authors have read and approved the final manuscript for submission.

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Not applicable

Conflict of interest

The investigation was undertaken without any financial conflicts of interest or any other commercial relationships that could be seen as such by any of the authors.