REVIEW
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Cathelicidin LL-37: mechanisms of action and research progress

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Author contributions

Zi-Ting Zhang designed the article structure and wrote the manuscript. Yi-Cheng Wu revised the text. Chun-Ming Dong guided the figure drawing and provided critical review of the article.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

AMPs, antimicrobial peptides; FPRL-1, formyl peptide receptor-like 1; MSCs, mesenchymal stem cells; *E. coli*, *Escherichia coli*.

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Abstract

Owing to their mechanism of action, antibiotics are prone to inducing drug resistance in the bacteria, viruses, and other pathogens. Therefore, there is an urgent need to develop a novel type of antimicrobial substance to safeguard human health. Antimicrobial peptides, members of the endogenous cathelicidin family in humans, possessing antibacterial, antiviral, and other related activities, represent promising potential alternatives to conventional antibiotics In terms of antibacterial properties. This review summarizes the relevant sources and secondary structure of LL-37 and elucidates that LL-37 not only exerts broad-spectrum antimicrobial effects through non-specific mechanisms such as disrupting pathogen cell membranes, which reduces the likelihood of resistance development, but also exhibits multiple biological activities, including immunomodulation, wound healing promotion, antitumor effects, and alleviation of osteoporosis. Currently, LL-37 shows broad application prospects in fields such as food preservation, pharmaceutical research and development, industrial biomaterial coatings, agricultural and crop disease resistance. However, LL-37 exhibits a dual role, capable of either inhibiting or promoting the proliferation of certain cancer cells depending on the context, which warrants further in-depth investigation using genetic engineering and other approaches. This article summarizes recent research progress on cathelicidin LL-37, outlines its mechanisms of action and application domains, aiming to provide a reference for future research advances on LL-37.

Keywords: cathelicidin LL-37; structure; antibacterial; anticancer; host defense

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Introduction

Antibiotics, recognized for their efficacy in inhibiting bacterial, viral, and fungal infections, have been extensively developed and utilized across various fields, including biomedicine, agricultural feed, and industrial production. However, with the passage of time and the continuous advancement of detection methods, the potential hazards and limitations of frequent antibiotic use have become increasingly apparent. Prolonged antibiotic use readily induces drug resistance in a wide range of harmful bacteria and viruses. Without timely intervention and improvement, there may be a phenomenon of "no medicine available" in the future. To promote public health and meet people's demand for health in the context of general health, the exploration and development of novel agents to replace or supplement conventional antibiotics are urgently needed.

Antimicrobial peptides (AMPs) are a class of naturally small organic molecules that play a crucial role in the defense systems of plants, animals, microorganisms, and even bacteria [1]. AMPs exhibit diverse structures, mostly common secondary structures such as α-helices or β-sheets, with their specific amino acid sequences dictating their functional properties [2]. They can combat many pathogens, including bacteria, fungi, and viruses. The unique mechanisms of AMPs involve disrupting pathogen cell membranes, interfering with intracellular processes, or inhibiting growth via other pathways, showing potent activity against Gram-positive and Gram-negative bacteria, viruses, and fungi [3]. Crucially, unlike antibiotics, AMPs often act via non-specific mechanisms, making them less likely to induce drug resistance. As early as 1980, American scientist Boman and other scientists first isolated animal-derived antimicrobial peptides, cecropins, from silkworm pupae [4]. Since then, more and more different types of AMPs have been discovered in plants, animals, bacteria, and other organisms, achieving commercial development. Cathelicidins are a family of antimicrobial peptides produced by mammals in response to pathogenic challenges. Cathelicidin LL-37, a key human member of this family, plays a vital role in enhancing host immunity and exhibits potential in cancer therapy (Figure 1). It can replace antibiotics and has great potential for development.

Currently, there has been considerable clinical development and research on LL-37, including investigations into its lytic effects on cell membranes, its inhibitory actions against cancer cells, the modulation of related signaling pathways, as well as the engineering and application of LL-37-derived short peptides. The potential application of LL-37 is continuously expanding and deepening [5].

Origin of cathelicidin LL-37

Cathelicidin LL-37 is widely distributed in various human tissues, including the skin, digestive tract, and cornea. Its precursor is the inactive human cationic antimicrobial peptide 18, which undergoes extracellular cleavage mediated by proteinase 3 to release the mature peptide. It consists of 37 amino acids derived from cathelicidin and is named LL-37 because its initial amino acid is leucine [6]. Cathelicidins are highly conserved across species [7]. Upon encountering pathogens or specific signals, local human cationic antimicrobial peptide 18 expression is upregulated, and the precursor is cleaved by serine proteases, such as proteinase 3, to generate the biologically active LL-37 [8]. The human antimicrobial peptide LL-37 is mainly produced by leukocytes and epithelial cells. Beyond its direct bactericidal activity, LL-37 can also inactivate host cells through a unique mechanism involving the induction of caspase-independent apoptosis [9].

Structure of cathelicidin LL-37

The structural conformation of LL-37 is highly dependent on its solvent environment. In aqueous water, the structure of LL-37 is an irregular helix, whereas under physiological conditions, its secondary structure adopts an α-helix. Its free amphipathic peptide segment consists of 37 residues, with the detailed sequence: LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLVPRTES [10], including 16 charged amino acids with a total net charge of +6 [11]. Schematic representations of its secondary and tertiary structures are depicted in Figure 2. Functionally, the N-terminal region is primarily associated with hemolytic activity, chemotaxis, and resistance to proteolysis, while the C-terminal region is crucial for its antimicrobial, anticancer, and antiviral activities [12]. Through infrared reflection-absorption spectroscopy and X-ray reflectometry, it can be detected that LL-37 is divided into two fragments at the buffer interface: LL-32 and LL-20, among which the activity of LL-32 is greater than that of LL-37 [13]. Structural analyses indicate that residues 1–13 contribute to hemolytic activity but are dispensable for antimicrobial function, whereas the C-terminal residues 32–37 are unstructured and appear to modulate proteolytic resistance and hemolytic potential [14].

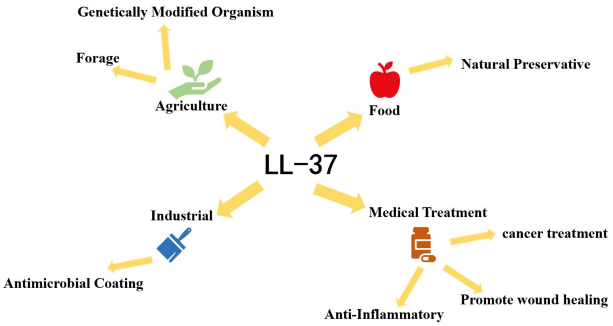

Figure 1 LL-37 related functions

Figure 2 LL-37 sequence model

Most of the translated LL-37 peptide segments will undergo relevant modifications to change the activity and stability of LL-37. Common peptide modifications include glycosylation, phosphorylation, acylation, and polyphenol conjugation [15]. The antimicrobial activity of LL-37 is largely determined by its secondary structure and cationic charge. If the lysine residues and the amino acid at the N-terminus of the protein are formylated, the positively charged lysine residues will be converted into neutral citrulline, which reduces the hemolytic activity of LL-37 and transforms the anti-inflammatory effect of LL-37 into a pro-inflammatory one [16].

Under physiological pH conditions, LL-37 tends to oligomerize, and the aggregated morphology determines the way LL-37 acts on bacterial cell membranes in the later stage, which improves the diversity [17].

Functional properties of cathelicidin LL-37

LL-37 exhibits a broad spectrum of biological activities. In addition to its primary function of preventing pathogenic bacterial infections, LL-37 can also promote cell proliferation, epithelial cell migration, and wound healing. The multiple functional activities of LL-37 promote one another, jointly maintaining tissue homeostasis and development [18]. Together with other antimicrobial peptides, LL-37 constitutes the first line of defense of the human immune system. By monitoring tumor transformation, LL-37 can activate formyl peptide receptor-like 1 (FPRL-1) accordingly, promoting the proliferation and release of immune lymphocytes [19]. For example, in gastric cancer, the formyl peptide family receptors activated by LL-37 can secrete substances that inhibit tumor activity, thereby promoting the treatment of gastric cancer [20]. However, studies have found that while LL-37 shows inhibitory effects on most cancer cells, it can promote the proliferation of a few cancer cells, accelerating the proliferation rate of cancer cells and endangering human health. Ovarian cancer is currently the most common gynecological disease, with inconspicuous latent symptoms, and it is generally easy to detect only in the advanced stage [21]. Mesenchymal stem cells (MSCs) can produce a variety of cell growth factors and promote cell proliferation. LL-37 recruits MSCs to the ovary through FPRL-1, enabling MSCs to exert relevant biological activities and promoting tumor proliferation and spread [22]. At the same time, numerous studies have reported that vitamin D can effectively promote the activation and expression of LL-37 in the body, making regulator of LL-37 in vitro [23].

LL-37 can enhance or inhibit the development of cancer through multiple signals [24]. Further research on the biological activity of LL-37 is necessary better to understand the role of LL-37 in tumor treatment.

Mechanism of action of cathelicidin LL-37

Cell permeabilization mechanism

The cell membrane of Gram-negative bacteria is primarily composed of lipids (constituting 40%–50% of its mass), proteins, and carbohydrates [25]. Its biological framework is a phospholipid bilayer, and the basic structure is composed of phospholipids, phosphatidylglycerol, and cardiolipins [26]. The anionic head groups of membrane phospholipids exhibit strong electrostatic attraction for the cationic N-terminal region of LL-37. Upon binding, LL-37 undergoes a conformational shift to form an amphipathic α-helix, facilitating deeper integration into the membrane. The hydrophilic groups enter the interior of lipid molecules, opening an ion channel and causing the substances in pathogenic bacteria to be excreted, ultimately leading to their death [27].

This non-specific mechanism of membrane disruption, driven largely by electrostatic and hydrophobic interactions, significantly reduces the propensity for bacteria to develop resistance.

The specific mechanism of action of LL-37 on cells can be divided into three models: barrel-stave model (Figure 3), carpet model (Figure 4), and toroidal-pore model (Figure 5). In the barrel-stave model, the oligomers formed by the polymerization of antimicrobial peptides encoded in the cell membrane are inserted into the lipid bilayer to form ion channels. External water enters the cell through the ion channels, leading to the leakage of intracellular substances, destroying the internal osmotic pressure of the cell, and finally damaging the integrity of the cell membrane, resulting in cell death [28]. In the toroidal-pore model, the α-helix of the peptide is directly embedded into the lipid bilayer, directly causing a disordered arrangement of phospholipids in the cell membrane and destroying the integrity of the cell membrane [29]. Different from the first two models, the carpet model does not directly damage the cell membrane or the interior of the cell. Instead, it forms a dense, carpet-like network structure on the surface of the bacterial cell membrane, combining with the bacterial cell membrane through electrostatic interactions, which induces the membrane's permeability to ions and subsequently causes changes in the membrane structure, leading to cell inactivation [30].

Non-targeted mechanism

The cell wall of bacteria is mainly composed of peptidoglycan and phospholipids, and the peptidoglycan layer is of great significance to the integrity of the bacterial cell membrane. AMPs can selectively bind to lipid II, a precursor molecule for cell wall synthesis, thereby inhibiting the formation of the cell wall and destroying the integrity of the cell membrane at the same time [31].

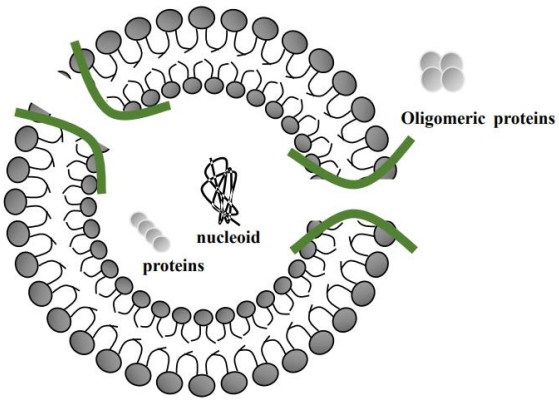

Figure 3 Barrel-stave model

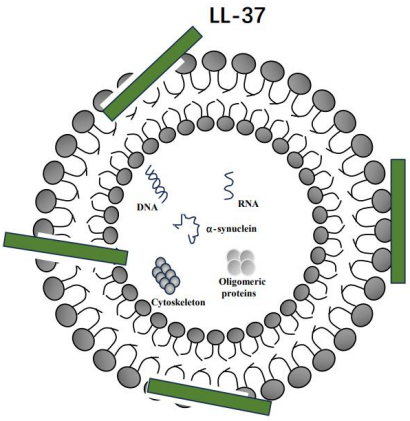

Figure 4 Carpet model

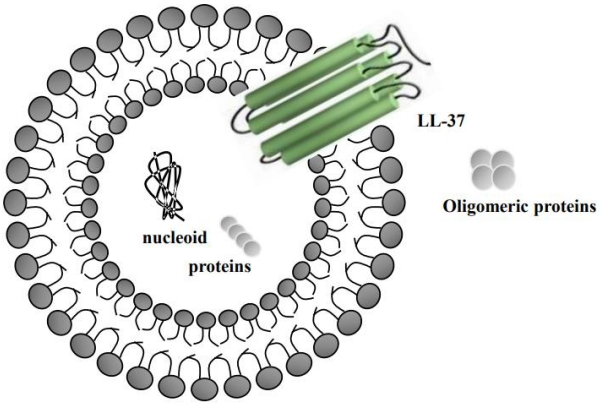

Figure 5 Toroidal-pore model

Immunomodulatory mechanism

Cathelicidin LL-37 is secreted by immune cells and participates in the differentiation and activation of related immune cells [32]. It serves as an important medium for the interaction between adaptive immunity and innate immunity, having a significant impact on cellular immune regulation. Its mature peptide is composed of two amino acid residues, starting with two leucine residues. LL-37 can regulate immunity, promote angiogenesis, wound healing, tumor growth, and alleviate osteoporosis. The pathogenesis of osteoporosis is due to the disorder of the dynamic balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption. LL-37 can promote osteoblast differentiation and inhibit osteoclast formation. LL-37 has been proven to enhance immune responses by inducing the production of specific cytokines and chemokines, and can indirectly promote the recruitment of inflammatory cells and immune cells by up-regulating the expression of chemokines. It can indirectly promote the recruitment of inflammatory cells and immune cells by upregulating the expression of chemokines and their corresponding receptors in macrophages. Additionally, LL-37 can promote neovascularization and epidermal re-epithelialization during the wound healing process. Therefore, AMPs can affect the process of bone metabolism through multiple pathways, thereby influencing the development of osteoporosis [33].

Applications of cathelicidin LL-37

Based on its unique antibacterial and antiviral mechanisms of action, cathelicidin LL-37 has been widely applied in various fields such as food, medicine, and agriculture (Table 1).

In food industry

LL-37 possesses potent antibacterial and antifungal properties. Its unique mechanism of action minimizes the development of resistance, making it an attractive natural preservative. Cheese is a perishable food, but adding LL-37-RW4 composite biopolymer films to cheese can effectively improve the freshness and storage time of cheese during preservation [34], which is a major breakthrough in food preservation. Obesity is also a key dietary concern in recent years. Enlarged adipocytes and ectopic fat produce and secrete various metabolic, hormonal, and inflammatory products, which damage organs such as arteries, heart, liver, muscles, and pancreas [35], endangering human life and health. Cathelicidin LL-37 can inhibit cell accumulation and hepatic steatosis by inhibiting the CD36 receptor [36], and this research finding provides new ideas for the development and utilization of related weight-loss drugs.

In medicine

Staphylococcus aureus, a prevalent pathogen in skin wounds, impedes healing and exhibits considerable drug resistance [37]. LL-37 demonstrates potent anti-staphylococcal and immunomodulatory activities. Treating mouse wounds with LL-37 can significantly reduce the number of *Staphylococcus aureus*, fibrin exudation, and show the presence of mature collagen tissue, indicating a good angiogenesis process and microvascular density, which can well promote wound healing and recovery [38].

Mastitis is the most common inflammatory disease of mammary tissue and surrounding connective tissue caused by bacterial infection in lactating women [39]. Traditional antibiotics cannot fundamentally solve the problem and are prone to inducing drug resistance mechanisms in both mothers and infants. The antimicrobial peptide

cathelicidin LL-37 has bacteriostatic and anti-inflammatory effects, and can prevent or alleviate mastitis by changing and regulating the balance of milk flora.

Current cancer treatments include chemotherapy, radiotherapy, and a combination of radiotherapy and chemotherapy, which produce cytotoxicity to cells to kill cancer cells. However, at the same time, related treatment methods attack all cells in the body indiscriminately, which easily leads to a decline in human resistance and the emergence of related drug-resistant cells [40]. LL-37 specifically recognizes targets on cancer cells through the charged protons at its terminal, killing cancer cells by destroying their cell membranes and activating related immune factors. This process enables it to achieve anti-cancer effects without harming other cells in the body [41].

In industry

The demand for high-performance, biocompatible materials is rising, particularly in the medical device sector. Implantable devices require robust antimicrobial strategies to prevent infection. LL-37-based coatings have been developed that effectively inhibit colonization by Gram-negative bacteria and other pathogens, thereby reducing infection risks associated with medical implants [42].

Furthermore, using cathelicidin LL-37 as a surface coating for related structures can effectively reduce the rejection reaction between these substances and the human body, while also inducing the regeneration of related tissues and organs. Combining LL-37 with surface-inert peptides or titanium alloys, after implantation into the body, can promote internal bone formation by recruiting MSCs and accelerate bone repair [43].

In the biofilm process, traditional detachable collagen/hyaluronic acid polyelectrolyte multilayers have strong bacterial adhesion, resulting in low membrane life. Modifying collagen/hyaluronic acid polyelectrolyte multilayers with LL-37 can effectively prevent microbial adhesion through the antimicrobial activity of LL-37 and neutralize the ability of *Escherichia coli* (*E. coli*) layers [44], which can be used in the design of antimicrobial coatings and engineered tissues in the future.

In agriculture

The application of LL-37 provides new ideas and potential therapeutic strategies for solving the increasingly serious problem of bacterial resistance in the fight against bacterial resistance. At the same time, it can improve the immunity of animal organisms. It has potential application value in the treatment of infectious diseases, cancer, etc.

Adding a small amount of antimicrobial peptides to chicken feed can effectively improve the number of colonies in the chicken intestine. It can reduce Gram-negative *E. coli* while effectively increasing the content of *Lactobacillus* and *Bifidobacterium* in the chicken cecum, effectively improving the colony environment in the chicken intestine, and increasing the chicken's feed conversion ratio (weight gain/feed intake) [45]. Adding antimicrobial peptides to the breeding of *Monopterus albus* can effectively improve the survival rate and immune function of *Monopterus albus*. In the experimental group, where antimicrobial peptides were added to *Monopterus albus* cultivation with an additional amount of 600 mg/kg, compared with the control group, where only normal breeding was carried out, the TP content in the serum of *Monopterus albus* in the experimental group was effectively increased by 16.1% [46].

In crops, introducing cathelicidin LL-37 into the expression gene sequence of Chinese cabbage through genetic engineering can effectively inhibit the expression of susceptibility-related genes in leaves and enhance the resistance of Chinese cabbage to bacteria and fungal viruses [47].

Opportunities and challenges

In recent years, the extraction methods of LL-37 can be roughly divided into chemical synthesis, synthesis from organisms, and genetic engineering. The first two methods have low extraction efficiency and high cost due to the instability of LL-37. Therefore, genetic engineering has emerged as the most viable method for large-scale production. *E. coli*, as an ideal model organism, has the advantages of fast reproduction, simple structure, and easy cultivation [48]. Combining the relevant expression sequence of LL-37 with *E. coli* plasmids has greatly increased the expression number of LL-37 and its stability in the host, providing raw material support for the further development of LL-37 [49]. At the same time, LL-37 can be used as an immunomodulator in allergic rhinitis and has been confirmed to be the cause of tissue damage in allergic rhinitis [50], providing new ideas for the treatment of allergic rhinitis. Meanwhile, the synergistic effect of LL-37 with other biomolecules and related signal transduction pathways remains to be studied in the future.

Table 1 Summary of LL-37 applications

Application	Function	Mechanism	Model system	Reference
In food industry	Food preservation (e.g., cheese)	Antibacterial, antifungal; unique mechanism reduces drug resistance.	Carpet model and toroidal pore model	[34]
	Potential anti-obesity agent	Inhibits the CD36 receptor, suppressing lipid accumulation and hepatic steatosis.	Non-pore mechanism	[36]
In medicine	Wound healing	Antiviral, antibacterial; reduces bacterial load, promotes angiogenesis and collagen formation.	Toroidal pore model	[38]
	Anti-cancer therapy	Specifically targets and disrupts cancer cell membranes; activates immune factors.	Toroidal pore model Barrel-stave model Non-pore mechanism	[41]
In industry	Medical device sector	Resists infection by Gram-negative bacteria.	Toroidal pore model	[42]
	Biomedical implant coatings	Reduces immune rejection, induces tissue regeneration; recruits mesenchymal stem cells to promote bone formation.	Non-pore mechanism	[43]
	Biofilm technology	Prevents microbial adhesion; neutralizes bacterial layers.	Toroidal pore model Barrel-stave model Carpet model	[44]
In agriculture	Animal feed additive	Improves gut microbiota (e.g., reduces *Escherichia coli*, increases probiotics); enhances immunity and growth.	Carpet model	[46]
	Crop disease resistance	Engineered into crops to enhance resistance against bacterial and fungal pathogens.	Genetic engineering	[47]

Conclusion

As the first line of defense of human immunity, cathelicidin LL-37 is of great significance for improving human immunity and treating related cancers in the future. Future research focusing on its molecular structure, structure-activity relationships, and precise mechanisms of action will be pivotal for unlocking its full potential across diverse sectors, including food science, medicine, and agriculture. Leveraging its broad-spectrum antimicrobial activity and unique, resistance-evading mechanism of action, LL-37 serves as a promising template for developing next-generation antimicrobial agents that could potentially supplement or replace conventional antibiotics. However, while exploring the broad applications of LL-37, significant attention must also be paid to the adverse effects and potential hazards it may cause in biological systems. Subsequent studies should further investigate the underlying causes of the adverse effects induced by cathelicidin LL-37 and the signaling pathways involved, fully leverage its antimicrobial and anti-cancer advantages, and continuously enhance the stability and diversity of LL-37's actions. It is hoped that through future research and development, LL-37 can realize industrial production and make relevant contributions to the progress and growth of the overall biological discipline.

With the continuous advancement of technology and biomolecular research techniques, we will gain a more comprehensive and in-depth understanding of LL-37 in the future. This will provide new therapeutic approaches for human diseases and offer more complete and safer safeguards for healthy living.

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