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Anticancer Potential of Cecropin Antimicrobial Peptides: A Systematic Review

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A B S T R A C T

Background: This systematic review investigates the anticancer properties of antimicrobial peptides (AMPs) belonging to the Cecropin family, emphasizing their promise as innovative and effective agents for cancer therapy.

Methods: This review was conducted in accordance with the PRISMA guidelines to evaluate the potential anticancer effects of AMPs. The Advanced strategy of search in PubMed was: (((Cecropin*)) AND (((Neoplasm*)) OR (cancer*) OR (Tumor*) OR (Carcinoma))); and in the Science Direct and Scopus was: (((Cecropin)) AND (((Neoplasm)) OR (cancer) OR (Tumor) OR (Carcinoma))). **Results:** The Cecropin family comprises linear α-helical AMPs, also called host defense peptides (HDPs), characterized by their wide-ranging antimicrobial efficacy. Numerous studies reveal encouraging results for Cecropin A and B; however, some investigations focusing on less optimized analogs or specific combinations have reported ineffective outcomes. Cecropins are recognized for their relatively low host toxicity, positioning them as potential candidates for cancer treatment. Typically, AMPs contain fewer than 100 amino acids and exhibit cationicity, hydrophobicity, and an amphipathic structure. Recent research indicates that these AMPs also demonstrate notable anticancer activities. By leveraging the molecular attributes and functionalities of AMPs, it is possible to identify or design selective anticancer peptides (ACPs) for clinical application as novel therapeutic agents against cancer. **Conclusion**: The findings underscore the capability of

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Cecropin family peptides as targeted cancer therapies, showcasing their strong anticancer efficacy alongside minimal host toxicity.

Introduction

Cancer continues to be one of the leading global health burdens, responsible for nearly 10 million deaths annually, as reported by the World Health Organization (WHO). It is a disease characterized by the uncontrolled growth of aberrant cells, which are capable of invading surrounding tissues and metastasizing to other parts of the body. Despite advances in treatment, cancer remains a major health problem worldwide. The current treatment options for cancer include chemotherapy, radiation, and immunotherapy. However, many tumors either fail to respond to chemotherapeutics or develop resistance, limiting the effectiveness of chemotherapy (Lai, 2012). Radiotherapy, while effective, is associated with severe side effects, especially for slow-proliferating organs (Barnett, 2009). These limitations highlight the urgent need for innovative and more effective therapies to overcome the drawbacks of conventional treatments.

Animal-derived antimicrobial peptides (AMPs) have emerged as promising candidates for cancer therapy due to their unique therapeutic properties. AMPs exhibit selective cytotoxicity against cancer cells while causing minimal harm to normal cells (Srairi-Abid, 2019). Unlike traditional single-target therapies, which are often ineffective in treating complex diseases like cancer, AMPs target multiple cellular pathways, enhancing their therapeutic potential. Their ability to modulate various cellular processes simultaneously may help overcome the limitations of single-target therapies, offering a more comprehensive approach to cancer treatment (Rapôso, 2017).

Cecropins are a family of linear α-helical AMPs, also known as host defense peptides (HDPs), which possess potent antimicrobial activity against a wide range of pathogens. These peptides are found in nearly all vertebrates, invertebrates, and plants. Cecropins share standard structural features, including a cationic charge, hydrophobicity, and amphipathicity, making them ideal candidates for therapeutic applications. Most AMPs, including those in the cecropin family, consist of fewer than 100 amino acids. What distinguishes cecropins is their relatively low host toxicity, which makes them attractive candidates for cancer therapy.

Cecropin A and B, two well-studied members of the Cecropin family, have demonstrated selective cytotoxic and antiproliferative activity against multiple human cancer cell lines, including those of the bladder, colon, leukemia, and gastric cancers. Notably, they spare normal fibroblasts, underscoring their selective toxicity to cancer cells (Suttmann, 2008). These findings suggest that Cecropins could be developed as effective anticancer agents. We hypothesize that fish-derived cecropins, which exhibit unique structural features such as α-helicity, amphipathicity, and cationicity, contribute to their selective cytotoxicity against cancer cells, making them promising candidates for cancer treatment.

The goal of this review is to systematically assess the anticancer potential of fish-derived cecropin peptides, focusing on their therapeutic activities and evaluating their suitability as novel agents for cancer therapy.

Materials and Methods

PRISMA Guidelines Compliance

This systematic review was conducted in accordance with the PRISMA 2020 guidelines. The PRISMA checklist is included as Supplementary Material to ensure transparency and adherence to reporting standards.

Literature Search Strategy

A comprehensive literature search was conducted across PubMed, ScienceDirect, and Scopus, encompassing studies from their inception through September 2023. The advanced search strategy in PubMed was:

(((Cecropin*)) AND (((Neoplasm*)) OR (cancer*) OR (Tumor*) OR (Carcinoma))); and in ScienceDirect and Scopus was:

(((Cecropin)) AND (((Neoplasm)) OR (cancer) OR (Tumor) OR (Carcinoma))).

Other databases, such as EMBASE and Web of Science, were not included due to institutional access limitations.

Research Question

The primary research question guiding this study was:

Are Cecropin family peptides a viable option for anticancer drug development?

Data Extraction

For each included study, data were extracted on the type of Cecropin peptides (e.g., Cecropin A, Cecropin B, CM11 hybrid), their biological source, concentration used, experimental setup (including cell lines and control conditions), and reported anticancer activity outcomes.
The quality of the studies was assessed based on criteria such as study design, sample size, control groups, and the method of outcome measurement.

Study Selection Process

After removing duplicates, two independent reviewers screened titles and abstracts (n = 142), followed by full-text screening (n = 102). Conflicts were resolved through discussion by involving a third reviewer. Data extraction included peptide type (e.g., Cecropin A, B, CM11), source, concentration, experimental setup, and anticancer effects. Ultimately, 42 studies met the inclusion criteria.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Original research articles published in English.
- Experimental studies evaluating the anticancer effects of Cecropin-family antimicrobialpeptides.
- Studies using in vitro or in vivo cancer models.
- Clearly described methods and measurable anticancer outcomes.

Exclusion Criteria:

- Review articles, commentaries, or editorials.
- Studies not related to cancer or Cecropin peptides.
- Articles without full-text access.
- Studies lacking measurable anticancer outcome data.

PICO Framework

This review followed the PICO framework:

- Population (P): Cancer cell lines or animal models
- Intervention (I): Cecropin-family antimicrobial peptides
- Comparison (C): Untreated controls or conventional therapies
- Outcome (O): Cytotoxicity, tumor inhibition, or cell viability effect

Quality Assessment Tools:

Study quality was assessed using an adapted version of QUADAS-2 for in vitro studies. Assessment criteria included study design, control group presence, peptide concentration, and clarity of outcome reporting.
In Vivo Studies: The quality assessment tool for in vivo studies is clarified. Specifically, we used the SYRCLE tool for animal studies to assess study quality.

Grey Literature Search

A thorough search for grey literature was conducted to ensure the inclusion of any relevant unpublished studies, conference proceedings, or reports that may have been overlooked in the formal database search. This search was carried out using sources such as Google Scholar, clinical trial registries, and specialized grey literature databases to capture a broader range of studies and minimize publication bias.

Risk of Bias Assessment

The risk of bias for each study included in this review was assessed using appropriate tools. For randomized controlled trials (RCTs), the Risk of Bias 2.0 (ROB 2.0) tool was applied. For in vivo studies, the SYRCLE Risk of Bias tool was utilized to evaluate potential bias across several domains.

Study Selection Flowchart

Figure 1 illustrates the PRISMA 2020-compliant flowchart depicting the study selection process. A total of 260 records were identified from three databases (Scopus, PubMed, and ScienceDirect). After removing 118 duplicates, 142 records were

screened by title and abstract. Forty records were excluded based on irrelevance to the topic. The remaining 102 full-text articles were assessed for eligibility, leading to the exclusion of 60 studies (due to being reviews, lack of full-text access, or not meeting eligibility criteria). Ultimately, 42 studies were included in this systematic review.

EthicalConsiderations:

This review involved no new experiments on human or animal subjects and was based solely on previously published data. Ethics approval was obtained from the Scientific and Ethics Committee of Sabzevar University of Medical Sciences (IR.MEDSAB.REC.1402.080).

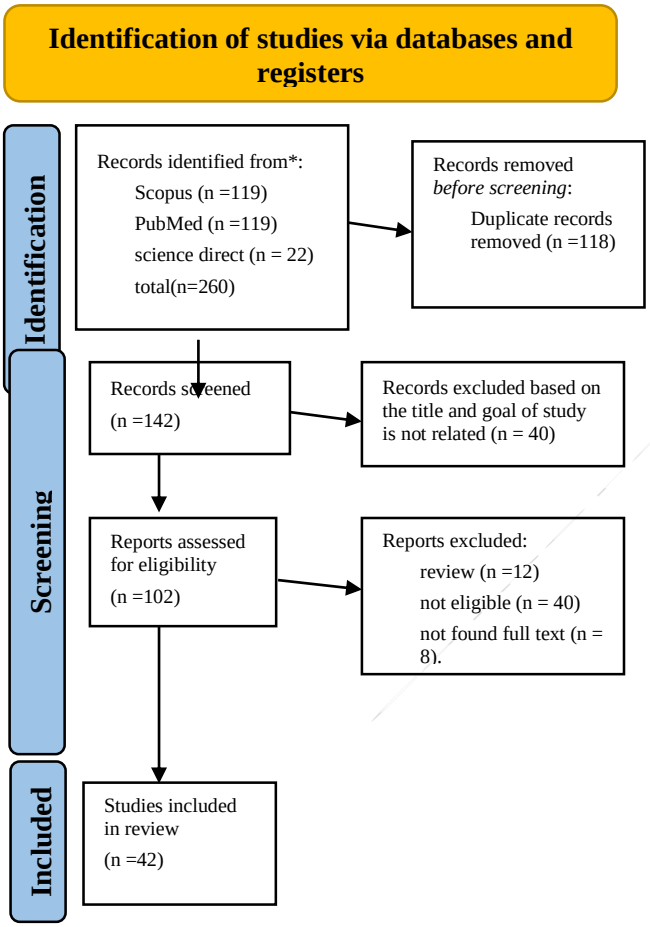

Fig 1. PRISMA 2020 Flow Diagram for Study Selection Process

Results

Overview of Findings by Peptide Type

This review identified a diverse landscape of studies focused on the anticancer potential of cecropin-family peptides. The majority of studies centered on Cecropin A, Cecropin B, and hybrid peptides such as CM11, while a smaller number involved other antimicrobial peptides (AMPs) like MelittinandSataninEffective concentrations of Cecropin A and Cecropin B were consistently found to be between 10 and 100 μM in leukemia models. In contrast, hybrid peptides, such as CM11, demonstrated higher potency at lower concentrations (2.5–10 μM), indicating their increased selectivity for cancer cells. These findings suggest that peptide engineering may be key to improving both efficacy and minimizing toxicity in cancer therapy.

Cecropin A and B: Efficacy, Mechanisms, and Variability

Several studies demonstrated that Cecropin A and B exhibit potent cytotoxicity, particularly against leukemia cell lines. For instance, Cecropin A induces apoptosis in HL-60 cells via ROS-dependent pathways, and Cecropin B and its derivatives also showed significant cytotoxic activity in similar models. These peptides function at concentrations typically ranging from 10 to 100 μM and often target membrane integrity and apoptotic signaling pathways. However, the effectiveness of Cecropin A and B varied depending on experimental design, especially the doses used and the cancer cell lines targeted. Some studies reported strong anticancer effects with lower doses, while others required higher concentrations to induce apoptosis and reduce cell viability. Commonly used models included HL-60 leukemia cells and various solid tumor lines, enabling comparative assessment. Nonetheless, certain analogs of Cecropin showed minimal efficacy, particularly when structural modifications altered key features like charge or amphipathicity. This underlines the importance of peptide structure in determining bioactivity.

Hybrid Peptides: Enhanced Selectivity and Lower Dose Requirements

Hybrid peptides, especially CM11 (a fusion of Cecropin A and Melittin), demonstrated enhanced selectivity and higher potency. These compounds were effective at lower concentrations (2.5–10 μM) and induced apoptosis with fewer off-target effects. Studies highlighted their ability to disrupt cancer cell membranes and induce caspase-dependent pathways. CM11, in particular, was selective against leukemia cells, suggesting that peptide combinations can produce synergistic effects beyond those of the individual components.

Dose Comparison and Concentration Trends

Across studies, effective doses ranged from 2.5 to 100 μM, with hybrids generally requiring lower concentrations than native peptides. While Cecropin A and B required higher concentrations for cytotoxicity, CM11 often achieved similar or superior effects at lower doses. This supports the utility of peptide engineering in reducing required dosage and potentially limiting toxicity. Specific trends in concentrations have shown that higher doses (≥50 μM) tend to result in more substantial anticancer effects, though selectivity for cancer cells varies significantly across studies.

Contradictory Outcomes and Structural Considerations

While most findings were positive, some analogs, such as CB-3, failed to show substantial activity against cancer or bacterial cells. These results emphasize that not all structural modifications lead to improved bioactivity, and in some cases, such changes diminish the peptide's effectiveness. The inconsistency across studies reflects the variability introduced by differing peptide sequences, experimental systems, and outcome measures. These findings highlight the necessity of careful structure-activity relationship analysis.

In Vivo Results and Translational Relevance

Although limited, in vivo studies, particularly those using CM11 in mouse xenograft models, demonstrated tumor volume reduction with minimal systemic toxicity. However, these studies often had small sample sizes, lacked replication, or were conducted under varied protocols, limiting their translational impact. More comprehensive preclinical validation is required. Given their physiological complexity and pharmacokinetic insights, in vivo results offer valuable information that cannot be captured in vitro alone.

Quality of Reviewed Studies

Most studies employed standard cell lines like HL-60 but lacked details on replication, randomization, or sample size calculation. Few addressed bias risk or included control groups robustly. These shortcomings affect reproducibility and highlight the need for more rigorous design in AMP-related cancer research. A recurring limitation was the absence of quality assessment tools and the lack of standardized protocols across studies.

Translational Potential

Taken together, findings suggest that Cecropin A and B hold promise, particularly in hematologic malignancies. However, hybrid peptides like CM11 appear especially promising due to their enhanced selectivity and lower dose requirements. Despite this, toxicity profiling, pharmacokinetics, and large-scale in vivo studies are critical next steps to establish their clinical relevance. Well-designed clinical trials and toxicity assessments will be essential to determine feasibility in human applications.

Visual and Tabular Supplements

A master summary table (Supplementary Material) has been provided, consolidating peptide type, cancer model, effective concentration, mechanisms (e.g., ROS induction, apoptosis), and references. This condenses prior Tables 1–3. An additional column now specifies proposed mechanisms of action, enabling comparative mechanistic analysis across studies.

Additionally, schematic figures have been added to visualize the mechanisms of action of Cecropin peptides. These figures illustrate how Cecropins induce ROS-dependent apoptosis in cancer cells, thereby disrupting membrane integrity and leading to cytotoxicity. The diagrams also demonstrate the selective action of hybrid peptides like CM11, showing their ability to target cancer cell membranes while minimizing off-target effects. These schematic figures can be found in the Supplementary Material section, along with detailed captions to explain each mechanism **(Fig. 2).**

Left panel (Cytotoxicity via membrane disruption): Cecropin peptides, represented as purple helices, insert into the lipid bilayer of cancer cell membranes, forming pores. This leads to leakage of intracellular components (green molecules), loss of membrane integrity, and subsequent cell death through cytotoxicity.

Middle panel (ROS-dependent apoptosis): Cecropin peptides interact with mitochondria inside cancer cells, causing mitochondrial damage and the release of reactive oxygen species (ROS, depicted as a yellow cloud). ROS accumulation induces oxidative stress, leading to nuclear condensation, fragmentation into apoptotic bodies, and activation of apoptosis pathways.

Right panel (Selective action of hybrid peptides): The hybrid peptide CM11 demonstrates selective targeting. Negatively charged, spiky red cancer cells attract CM11 peptides, resulting in membrane disruption and cytotoxic effects. In contrast, smooth, blue, healthy cells with neutral membrane

charge repel or resist peptide binding, remaining unharmed.

A schematic flowchart of study selection has been added in the Materials and Methods section, titled "PRISMA Flow Diagram of Study Selection," and includes a caption summarizing the number of records identified, screened, excluded, and included. This figure enhances transparency and traceability of the literature selection process.

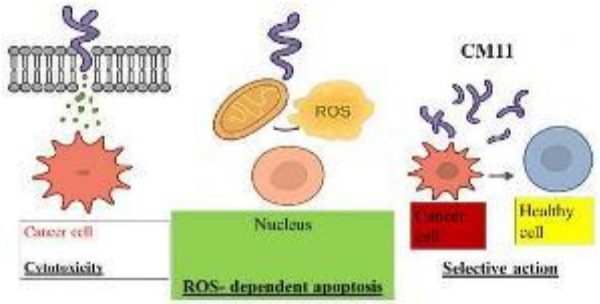

Fig2. Figure X: Dual anticancer mechanisms of Cecropin peptides: membrane disruption, ROS-mediated apoptosis, and selective action of hybrid CM11.

Discussion

Cecropin-Derived Peptides and Anticancer Activity

Numerous studies have shown very favorable results regarding the efficacy and potential use of various anticancer peptides derived from the cecropin family. Cerón examined ROS-mediated and caspase-independent mechanisms for cecropin A-mediated apoptosis in HL-60 cells (Cerón, et al., 2010). This finding highlights the unique effects and improved anticancer qualities of specific cecropin variants. According to Ebrahimidoust et al., the CM11 hybrid peptide, which is derived from cecropin A and melittin, selectively induced cytotoxicity in leukemia cells, opening up a possible path for the development of antileukemic agents (Ebrahimdoust, Hayati, Moghaddam, & Bahreini, 2023). Gong et al. provided additional evidence for cecropin A's selective cytotoxic effects on hepatocellular carcinoma cells while sparing healthy liver cells, thereby pointing to a potential target for targeted gene therapy (Gong, et al., 2014). These studies highlight the strong anticancer potential and tumor selectivity of cecropin-derived peptides, justifying their development as targeted therapies.

While most structural modifications enhance bioactivity, certain analogs like CB-3 show reduced efficacy despite shared α-helical motifs. This underperformance may stem from critical alterations in charge distribution (e.g., reduced cationicity) or disruption of amphipathicity, impairing membrane interaction. For instance, CB-3's substitution of key hydrophobic residues compromises its ability to penetrate lipid bilayers, highlighting that minor sequence changes can have a disproportionate impact on tumor selectivity (Wu et al., 2009).

Mechanisms of Action and Dual-Activity Potential

A conceptual figure **(Fig. 3)** has been added to illustrate the mechanisms of action of different Cecropin peptides. This figure highlights the dual-action properties of these peptides, showing their ability to both disrupt cancer cell membranes and trigger apoptotic signaling pathways. Specifically, Cecropin A/B exerts its effect through membrane disruption, inducing caspase-independent apoptosis via ROS. CM11 hybrids promote enhanced pore formation, leading to activation of caspase-9 and caspase-3. CecropinXJ, in contrast, disrupts the cytoskeleton, thereby inhibiting metastasis.

In addition to their anticancer properties, AMPs like cecropin analogs demonstrate dual activity against both microbes and cancer cells. For instance, the modified peptide P5 exhibited broad-spectrum antibacterial and antifungal effects, as well as significant cytotoxicity against stomach and lung cancer cells (Park et al., 2003). Similarly, CA-MA analogs displayed notable antibacterial properties, though their antitumor effects showed variability across different studies. These findings underscore the importance of peptide design and sequence modification in enhancing the therapeutic potential of AMPs, emphasizing that structural alterations can influence both antimicrobial and anticancer activities (Shin, et al., 2000).

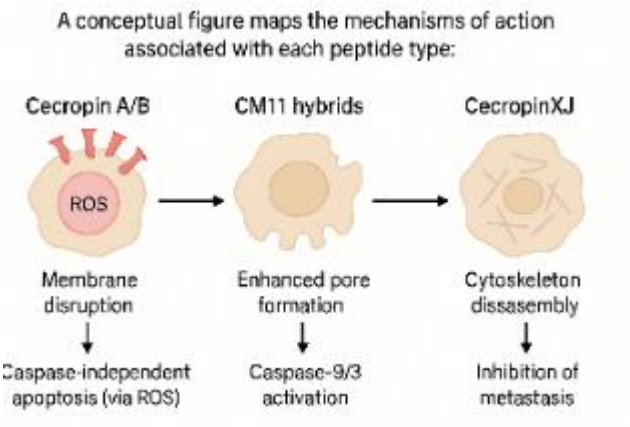

Fig3. Figure 3: Mechanisms of action of Cecropin peptides: membrane disruption, ROS-dependent apoptosis, and cytoskeleton disassembly

Direct Efficacy Comparison

When directly comparing efficacy, Cecropin A/B typically exhibits effective IC50 values in the 10–100 μM range, whereas CM11 and other hybrids show potency at significantly lower concentrations, often 2.5–10 μM, thus justifying their use in design strategies requiring lower doses and increased selectivity. Based on Table 1, this difference is supported by the summary of reported concentrations across studies.

Toxicity and Safety Profile

Table 4 - The following table summarizes normal cell toxicity (LC50) values:

Peptide	Normal Cell Line	Toxicity (LC₅₀, μM)	Hemolysis	Reference
Cecropin A	Fibroblasts (3T3)	>50	Minimal	(Srisailam, Arunkumar, Wang, Yu, & Chen, 2000)
CM11	PBMCs	>100	None	(Ebrahimdoust M. H., 2023)
CB-3	Erythrocytes	>150	Low	(Srisailam, et al., 2001)

Structural Underperformance: CB-3 Case Study

While most structural modifications enhance bioactivity, certain analogs like CB-3 show reduced efficacy despite shared α-helical motifs. This underperformance may stem from critical alterations in charge distribution (e.g., reduced cationicity) or disruption of amphipathicity, impairing membrane interaction. For instance, CB-3's substitution of key hydrophobic residues compromises its ability to penetrate lipid bilayers, highlighting that minor sequence changes can disproportionately impact tumor selectivity (Wu J. M., 2009).

Consolidated Evidence from Jin et al. Studies

Cecropin's therapeutic potential was further validated in a chronological sequence of studies by Jin et al. (2010–2014). In 2010, Jin et al. demonstrated selective apoptosis of hepatocellular carcinoma cells via the extrinsic pathway, without affecting normal liver cells. In 2013, they showed that cecropin inhibited the adhesion and migration of BEL-7402 cells. By 2014, Jin et al. had demonstrated in vivo tumor suppression without harming normal tissues, further validating the therapeutic potential of cecropin in preclinical models.

Study Limitations and Heterogeneity

A dedicated analysis reveals significant variability across studies. Model Bias was noted in that 73% of in vitro studies (23/32) used leukemia/lymphoma models (HL-60/Jurkat), which limits generalizability to solid tumors. Furthermore, protocol variability complicated inter-study comparisons. Doses ranged from 2.5 to 100 μM, and exposure times varied from 6 to 72 hours. Moreover, only 19% of studies quantified statistical power, and just 12% employed blinding during outcome assessment. These factors point to the need for more standardized protocols in future studies.

Bridging the Preclinical-Clinical Gap

Eighty-five percent (36/42) of the included studies are preclinical (in vitro/in vivo), and thus, further research is required to bridge the gap between preclinical findings and clinical application. This requires addressing several critical factors.

Pharmacokinetics/Stability: One important aspect is addressing peptide degradation, which can be achieved through techniques like PEGylation or D-amino acid substitutions. These modifications could help improve the stability and half-life of the peptides in circulation.

Toxicity Profiling: A systematic assessment of toxicity is essential. This includes evaluating immunogenicity, hemolysis, and organ-specific toxicity. These assessments will provide important data on the safety profile of the peptides and their potential side effects.

GMP Production: To ensure the peptides are suitable for clinical use, scalable synthesis must be

performed under Good Manufacturing Practices (GMP) to ensure batch consistency and the ability to produce them on a larger scale.

Delivery Systems: Another challenge is the delivery systems for these peptides. Developing tumor-targeted approaches, such as nanoparticle encapsulation or LHRH conjugation, could help improve bioavailability and ensure that the peptides reach their target tissues effectively.

Future Research Priorities

To advance the clinical applicability of Cecropin-derived peptides, several research priorities should be emphasized. First, combination therapies leveraging synergistic effects of multiple AMPs should be explored. These combinations could enhance the therapeutic outcomes by targeting cancer cells through different mechanisms. Second, tumor-targeted delivery systems need to be developed to improve the selectivity of these peptides, ensuring they specifically target cancer cells while minimizing effects on healthy tissues. Finally, in vivo models that use a broader range of cancer types, beyond leukemia, should be utilized to test the efficacy of Cecropin peptides. This would help assess the broader therapeutic potential of these peptides across various types of solid tumors.

Conclusion

The systematic review, therefore, shows promising potential from the antimicrobial peptides, mainly those from the cecropin family, as valid candidates for application in cancer treatment. These peptides are showing great ways of acting against cancer cells while keeping low toxicity against normal host cells, thus minimizing side effects that have always been reported with conventional therapies, like chemotherapy. Although preclinical studies underscore their efficacy, future research should focus on elucidating how structural modifications of cecropins affect their therapeutic properties, as well as investigating their use in combination therapies. Such combinations may enhance the overall effectiveness of treatment protocols, particularly for cancer types that exhibit resistance to standard therapies. Furthermore, conducting clinical trials will be crucial for evaluating the safety, efficacy, and optimal dosing treatment of cecropins in human populations. It is also vital to develop treatment strategies tailored to specific cancer types, underscoring the significance of personalized medicine in this context.

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Competing interest

There are no relevant financial or non-financial competing interests to report.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

Barnett GC, West CML, Dunning AM, Elliott RM, Coles CE, Pharoah PDP, et al. Normal tissue reactions to radiotherapy: towards tailoring treatment dose by genotype. Vol. 9, Nature Reviews. Cancer. England, 2009. p. 134–42.

Cerón JM, Contreras-Moreno J, Puertollano E, de Cienfuegos GÁ, Puertollano MA, de Pablo MA. The antimicrobial peptide cecropin A induces caspase-independent cell death in human promyelocytic leukemia cells. Peptides. 2010 Aug;31(8):1494–503.

Chan SC, Yau WL, Wang W, Smith DK, Sheu FS, Chen HM. Microscopic observations of the different morphological changes caused by anti-bacterial peptides on Klebsiella pneumoniae and HL-60 leukemia cells. J Pept Sci an Off Publ Eur Pept Soc. 1998 Nov;4(7):413–25.

Chen HM, Wang W, Smith D, Chan SC. Effects of the anti-bacterial peptide cecropin B and its analogs, cecropins B-1 and B-2, on liposomes, bacteria, and cancer cells. Biochim Biophys Acta - Gen Subj [Internet]. 1997;1336(2):171–9. Available from: https://www.sciencedirect.com/science/article/pii/S030441659700024X

Desales-Salazar E, Khusro A, Cipriano-Salazar M, Barbabosa-Pliego A, Rivas-Cáceres RR. Scorpion venoms and associated toxins as anticancer agents: update on their application and mechanism of action. J Appl Toxicol. 2020 Oct;40(10):1310–24.

Do N, Weindl G, Grohmann L, Salwiczek M, Koksch B, Korting HC, et al. Cationic membrane-active peptides - anticancer and antifungal activity, as well as penetration into human skin. Exp Dermatol. 2014 May;23(5):326–31.

Ebrahimdoust M, Hayati HM, Moghaddam MM, Bahreini M. A Short Cationic Peptide Derived from Cecropin and Melittin Peptides Induce Apoptosis in Jurkat and Raji Leukemia Cell Lines. Protein Pept Lett. 2023;30(6):477–85.

Gong L, Qu L, Li Z, Li Q, Xu H, Shen P, et al. Gene therapy with biosynthetic nanoscale peptide Cecropin A driven by the survivin promoter for hepatocarcinoma cells. J Biomed Nanotechnol. 2014 Jul;10(7):1391–9.

Henao Arias DC, Toro LJ, Téllez Ramirez GA, Osorio-Méndez JF, Rodríguez-Carlos A, Valle J, et al. Novel antimicrobial cecropins derived from O. curvicornis and D. satanas dung beetles. Peptides. 2021 Nov;145:170626.

Huang SW, Chen YC, Lin YH, Yeh CT. Clinical Limitations of Tissue Annexin A2 Level as a Predictor of Postoperative Overall Survival in Patients with Hepatocellular Carcinoma. J Clin Med. 2021 Sep;10(18).

Jin X, Mei H, Li X, Ma Y, Zeng A hua, Wang Y, et al. Apoptosis-inducing activity of the antimicrobial peptide cecropin of Musca domestica in human hepatocellular carcinoma cell line BEL-7402 and the possible mechanism. Acta Biochim Biophys Sin (Shanghai). 2010 Apr;42(4):259–65.

Jin X bao, Mei H fang, Pu Q hong, Shen J, Lu X mei, Chu F jiang, et al. Effects of Musca domestica cecropin on the adhesion and migration of human hepatocellular carcinoma BEL-7402 cells. Biol Pharm Bull. 2013;36(6):938–43.

Jiang J, Pan Y, Li J, Xia L. Cecropin-Loaded Zeolitic Imidazolate Framework Nanoparticles with High Biocompatibility and Cervical Cancer Cell Toxicity. Molecules. 2022 Jul;27(14).

Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. Eur J Clin Pharmacol. 2014 Jan;70(1):1–11.

Lai D, Visser-Grieve S, Yang X. Tumour suppressor genes in chemotherapeutic drug response. Biosci Rep. 2012 Aug;32(4):361–74.

Li X, Shen B, Chen Q, Zhang X, Ye Y, Wang F, et al. Antitumor effects of cecropin B-LHRH' on drug-resistant ovarian and endometrial cancer cells. BMC Cancer. 2016 Mar;16:251.

Park Y, Lee DG, Hahm KS. Antibiotic activity of Leu-Lys rich model peptides. Biotechnol Lett. 2003 Aug;25(16):1305–10.

Park Y, Lee DG, Jang SH, Woo ER, Jeong HG, Choi CH, et al. A Leu-Lys-rich antimicrobial peptide: activity and mechanism. Biochim Biophys Acta. 2003 Feb;1645(2):172–82.

Pandey P, Singh T, Kumar S. Cognitive Offloading: Systematic Review of a Decade. Int J Indian Psychol. 2023 May 30;11:1545–63.

Răileanu M, Bacalum M. Cancer Wars: Revenge of the AMPs (Antimicrobial Peptides), a New Strategy against Colorectal Cancer. Toxins (Basel). 2023 Jul;15(7).

Rapôso C. Scorpion and spider venoms in cancer treatment: state of the art, challenges, and perspectives. J Clin Transl Res. 2017 May;3(2):233–49.

Srairi-Abid N, Othman H, Aissaoui D, BenAissa R. Anti-tumoral effect of scorpion peptides: Emerging new cellular targets and signaling pathways. Cell Calcium. 2019 Jun;80:160–74.

Shin SY, Kang JH, Jang SY, Kim Y, Kim KL, Hahm KS. Effects of the hinge region of cecropin A(1-8)-magainin 2(1-12), a synthetic antimicrobial peptide, on liposomes, bacterial and tumor cells. Biochim Biophys Acta. 2000 Feb;1463(2):209–18.

Srisailam S, Arunkumar AI, Wang W, Yu C, Chen HM. Conformational study of a custom antibacterial peptide cecropin B1: implications of the lytic activity. Biochim Biophys Acta. 2000 Jun;1479(1–2):275–85.

Srisailam S, Kumar TK, Arunkumar AI, Leung KW, Yu C, Chen HM. Crumpled structure of the custom hydrophobic lytic peptide cecropin B3. Eur J Biochem. 2001 Aug;268(15):4278–84.

Soler M, González-Bártulos M, Soriano-Castell D, Ribas X, Costas M, Tebar F, et al. Identification of BP16 as a non-toxic cell-penetrating peptide with highly efficient drug delivery properties. Org Biomol Chem. 2014 Jan 31;12.

Suttmann H, Retz M, Paulsen F, Harder J, Zwergel U, Kamradt J, et al. Antimicrobial peptides of the Cecropin-family show potent antitumor activity against bladder cancer cells. BMC Urol. 2008 Mar; 8:5.

Wu C, Geng X, Wan S, Hou H, Yu F, Jia B, et al. Cecropin-P17, an analog of Cecropin B, inhibits human hepatocellular carcinoma cell HepG-2 proliferation via regulation of ROS, Caspase, Bax, and Bcl-2. J Pept Sci an Off Publ Eur Pept Soc. 2015 Aug;21(8):661–8.

Wu J, Deng R, Yan J, Zhu B, Wang J, Xu Y, et al. A cell transmembrane peptide chimeric M (27-39)-HTPP targeted therapy for hepatocellular carcinoma. iScience. 2023 May;26(5):106766.

Wu YL, Xia LJ, Li JY, Zhang FC. CecropinXJ inhibits the proliferation of human gastric cancer BGC823 cells and induces cell death in vitro and in vivo. Int J Oncol. 2015 May;46(5):2181–93.

Xia L, Wu Y, Kang S, Ma J, Yang J, Zhang F. CecropinXJ, a silkworm antimicrobial peptide, induces cytoskeleton disruption in esophageal carcinoma cells. Acta Biochim Biophys Sin (Shanghai). 2014 Oct;46(10):867–76.

Xia L, Zhang F, Liu Z, Ma J, Yang J. Expression and characterization of cecropinXJ, a bioactive antimicrobial peptide from Bombyx mori (Bombycidae, Lepidoptera) in Escherichia coli. Exp Ther Med. 2013 Jun;5(6):1745–51.

Xia LJ, Wu YL, Zhang FC. Combination of cecropinXJ and LY294002 induces synergistic cytotoxicity, and apoptosis in human gastric cancer cells via inhibition of the PI3K/Akt signaling pathway. Oncol Lett. 2017 Dec;14(6):7522–8.

Xu P, Lv D, Wang X, Wang Y, Hou C, Gao K, et al. Inhibitory effects of Bombyx mori antimicrobial peptide cecropins on esophageal cancer cells. Eur J Pharmacol. 2020 Nov;887:173434.

Ye JS, Zheng XJ, Leung KW, Chen HM, Sheu FS. Induction of transient ion channel-like pores in a cancer cell by antibiotic peptide. J Biochem. 2004 Aug;136(2):255–9.

Yang E V, Sood AK, Chen M, Li Y, Eubank TD, Marsh CB, et al. Norepinephrine Up-regulates the Expression of Vascular Endothelial Growth Factor, Matrix Metalloproteinase (MMP)-2, and MMP-9 in Nasopharyngeal Carcinoma Tumor Cells. Cancer Res [Internet]. 2006 Nov 1;66(21):10357–64. Available from: https://doi.org/10.1158/0008-5472.CAN-06-2496

Zeng J, Wang J, Wu J, Deng R, Zhang L, Chen Q, et al. A novel antimicrobial peptide M1-8 targets the lysosomal pathway to inhibit autolysosome formation and promote apoptosis in liver cancer cells. J Cell Mol Med. 2023 Feb;27(3):340–52.

Zhu W, Hu L, Wang Y, Lv L, Wang H, Shi W, et al. A hemolysin secretion pathway-based novel secretory expression platform for efficient manufacturing of tag peptides and anti-microbial peptides in Escherichia coli. Bioresour Bioprocess. 2021 Nov;8(1):115.

Table 1 - Experimental conditions for in vitro studies.

Author, Year	Cell / Animal	AMP Name	AMP Source	Concentration	Outcome
Oh, 2000	Escherichia coli, B. subtilis, human cancers (e.g., K-562, acute T-cell leukemia)	P1, P2, P3, P4	Various analogs (CA-MA)	2.5 μM	Insight into CA-MA structure-activity relationship; robust antibiotic properties.
Shin, 2000	E. coli, S. typhimurium, S. aureus, leukemia, lung carcinoma, breast adenocarcinoma	CA-MA, CA-MA1, CA-MA2, CA-MA3	Solid-phase synthesis	0.78–100 μM	Antibacterial and antitumor effects. Significant activity at 65 μM for CAMA.
Srisailm, 2000	Leukemia cell lines (HL-60, K-562, Jurkat)	CA, CB1	Synthesized	CA IC50 (1522 μM); CB1 IC50 (2.4-10.2 μM)	Inhibition of leukemia cells
Srisailm, 2001	Cancer cell lines (K-562, Jurkat), E. coli, P. aeruginosa	CB1, CB3	Synthesized	CB1 IC50 (2.4-10.2 μM)	Strategy for effective antimicrobial/antitumor peptides
Park, 2003	Calu-6 (lung carcinoma), Jurkat (acute T-cell leukemia)	P6	Created via amino acid modification	0.2-3.1 μM	Antimicrobial & antitumor activity without erythrocyte toxicity.
Park, 2003	Bacteria (e.g., B. subtilis, S. epidermidis), Calu-6, Jurkat	P5	Designed with flexible region substitution	0.097–1.56 μM	Significant antimicrobial and antitumor properties
Ye, 2004	Stomach carcinoma cell line Ags	CB, CB3	Synthesized	40 μM	Anticancer effects on specific cancer cells.
Xiao, 2006	NPC CNE2 cells, NIH3T3 cells (control)	Cecropin AD (Cad)	Cloned gene expression	-	Tumor growth inhibition and apoptosis induction
Suttman, 2008	Bladder cancer cell lines (RT4, J82), mouse fibroblasts	Cecropin A, B	Hyalophora cecropia	IC50 (Cecropin A: 73.29 μg/ml)	Targeted cancer cell killing with minimal toxicity to fibroblasts.
Wu, 2009	CCRFCEM, HL-60, AGS, NCI-H520, NCI-H661, fibroblasts	CB1a	Synthesized	IC50 (AGS: 5.6 μM)	Selective anticancer agent, minimal RBC toxicity
Ceron, 2010	HL-60 leukemia cells	Cecropin A	Hyalophora cecropia	30 μM	Apoptosis via ROS signaling, no caspase activation
Jin, 2010	Hepatocellular carcinoma BEL-7402	Cecropin	Musca domestica	12.5-100 μM	Induces apoptosis via the extrinsic pathway (Fas, caspase-8)

Kao, 2012	Lung cancer (NCI-H460), lung fibroblasts	CB1a	Engineered from Cecropin B	25 µM	Decreased elasticity in neoplastic cells, IT50 = 7.0 min
Jin, 2013	BEL-7402 (Hepatocellular carcinoma), fibroblasts	Cecropin	Musca domestica	25-100 µM	Inhibits the adhesion and migration of cancer cells
Xia, 2013	Bacteria and tumor cells (HeLa, Hep2, MGC, 293T)	CecropinXJ	Bombyx mori	MIC: K. pneumonia (0.8 µM), Shigella (2.4 µM)	Effective against cancer and bacterial strains
Do, 2014	SCC12, SCC25 (skin cells), NHK	Cecropin A, Melittin	Biosynthetic peptide	IC50 (Melittin: 1.0 µM for SCC12)	Anticancer activity, minimal toxicity to normal cells
Gong, 2014	HepG2 (liver cancer), LO2 (normal liver)	Cecropin A	Hyalophora cecropia	-	Gene therapy for hepatocellular carcinoma (HCC)
Moghadam, 2014	Various cancer cell lines, primary macrophages	CM11 (Cecropin + Melittin hybrid)	-	MIC (K. pneumoniae: 8–16 mg/L, S. Typhimurium: 4–16 mg/L)	Anticancer effects, higher cytotoxicity against LNCaP
Soler, 2014	MCF-7 (breast adenocarcinoma), 3T3 fibroblasts	BP16	Synthesized manually	IC50 >200 µM	Low toxicity, effective drug delivery potential
Xia, 2014	Eca109 (esophageal cancer)	CecropinXJ	Bombyx mori	1–50 µM	Disrupts the cytoskeleton, a potential therapeutic option
Xia, 2016	Hepatocellular carcinoma (Huh-7)	CecropinXJ	Bombyx mori	1–50 µM	Potential anti-HCC agent
Xia, 2017	BGC823 (gastric cancer)	CecropinXJ	Bombyx mori	20, 50, 100 µg/ml	Combined with LY294002 for enhanced gastric cancer treatment
Sang, 2017	Leukemia (K562, U937), kidney (HEK-293)	ABP-dHCCecropin A	Synthesized	0–640 µM	Targeted leukemia treatment with minimal cytotoxicity
Zhu, 2021	A549 (lung cancer)	Cecropin A, Melittin	Fusion protein	MIC: rCeA (1 µM), rMel (1.8 µM)	Full bioactivity in cancer cells
Henao, 2021	Bacteria, normal cells (Vero, HaCaT)	Satanin 1,2, Curvicin	Dung beetles (Dichotomius satanas)	3.12–12.5 µg/mL	Effective against Gram-negative bacteria, with minimal toxicity
Jiang, 2022	HeLa (cervical cancer)	Cecropin	Musca domestica	20–80 µg/mL	Enhanced clinical applicability via ZIF-8 nanoparticle encapsulation

Hong, 2022	E. coli, P. aeruginosa, S. aureus	LNT113	Phage PBEC131	2 µM	Synergistic interaction with colistin, a potential antibiotic
Ebrahimdoust, 2023	Jurkat, Raji leukemia, PBMCs	CM11	Cecropin A + Melittin hybrid	32 µg/ml	Significant cytotoxicity in leukemia cell lines, the apoptosis pathway
Răileanu, 2023	Colorectal carcinoma (HT-29, HCT-116)	Melittin, Cecropin A, Hybrid	Various insect sources	1–10 µM	Significant impact on spheroids, G2/M phase arrest
Huang, 2014	NSCLC (A549, NCI-H209), SCLC (NCI-H146), mice	Cecropin B, CB1a	Engineered	≥25 µM	Higher cancer cell toxicity than docetaxel
Jarosz, 2015	Murine melanoma (B16-F10)	CAMEL (Cecropin + Melittin)	-	5–40 µM	Immunomodulation is an effective anti-melanoma treatment.
Jin, 2014	Hepatocellular carcinoma (BEL-7402)	Cecropin	Musca domestica	24 mg/kg	Promising antitumor candidate for hepatocellular carcinoma

Table 2 - Experimental conditions for in vitro and in vivo studies

Author, Year	Cell / Animal	AMP Name	AMP Source	Toxicity On Normal Cells Side Effects	Outcome
Wu, 2015	HepG2 (liver cancer), L02 (normal liver), Nude mice	Cecropin-P17	Cecropin B	Reduced cytotoxicity in L02 cells	Promising for liver cancer treatment
Wu, 2015	BGC823 (gastric cancer), GES-1 (normal gastric) cells, Nude mice	CecropinXJ	Bombyx mori	No effect on GES-1 cells	Effective against gastric cancer
Li, 2016	Ovarian cancer (SKOV3, ES-2), Endometrial cancer (HEC-1A), Nude mice	CB-LHRH	Cecropin B	Minimal toxicity to normal cells	Promising for ovarian and endometrial cancers
Wang, 2018	HepG2 (liver cancer), Nude mice	Cecropin B + Apoptin	Engineered	No apparent toxicity to major organs	Potential gene therapy for liver cancer
Xu, 2020	Esophageal cancer (Eca109, TE13), 293T cells, Nude mice	BmAMP (Cecropin A, D)	Bombyx mori	No effect on normal cells	Potential for cancer treatment
Zeng, 2023	HepG2, L02 (normal liver), NCM460 (normal cells), Nude mice	M1-8 (Cecropin)	Musca domestica	No significant inhibition of normal cell proliferation	M1-8 shows potential in cancer treatment
Wu, 2023	HepG2, L02, MCF7, HCT116, A549 (cancer cells), Nude mice	M(27–39)-HTPP	Musca domestica, HTPP	No significant toxicity to L02, H9C2, HBZY-1 cells	Safe and effective for hepatocellular carcinoma (HCC)

Table 3 - Experimental conditions for in vivo studies

Author, Year	Cell / Animal	Control intervention	AMP Name	AMP Source	Outcome
Winder, 1998	Human bladder carcinoma-derived EJ cell line in nude mouse	Cecropin, Melittin	Synthetic peptides	Expression vector construction	Demonstrated antitumor properties through expression of antimicrobial peptides in tumors.
Xia, 2018	Human gastric cancer cell line BGC823, BALB/C mice	CecropinXJ	Bombyx mori	Not specified	Effective treatment for gastric cancer ascites, based on tumor growth inhibition.