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ORIGINAL RESEARCH ARTICLE

Clinical efficacy, safety, and pharmacologic determinants of antimicrobial peptides: A systematic review and meta-analysis

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Abstract

Introduction: Antimicrobial resistance poses an escalating global health threat, driving the need for alternative therapeutic strategies beyond conventional antibiotics. Despite extensive preclinical research, the clinical performance of these agents remains incompletely characterized.

Objective: This systematic review and meta-analysis synthesize and evaluate clinical efficacy, safety, and pharmacologic determinants of antimicrobial peptide therapeutics in human studies, and determine their comparative performance against standard-of-care treatments.

Methods: A comprehensive search of PubMed, Embase, Web of Science, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform identified eligible clinical studies published between January 2000 and January 2026. Randomized controlled trials and comparative clinical studies reporting clinical or microbiologic outcomes were included in the quantitative meta-analysis. Early-phase, single-arm, or non-comparative studies were synthesized qualitatively. A random-effects model was used to estimate pooled risk ratios (RRs) for clinical cure, and heterogeneity was assessed using the I^2 statistic.

Results: Six comparative clinical studies involving 1,418 participants were included in the meta-analysis. Pooled analysis demonstrated no statistically significant difference in clinical cure between peptide-based therapeutics and standard-of-care treatments (RR 1.06, 95% confidence interval: 0.97–1.17), with moderate heterogeneity ($I^2 = 64.7\%$). Early-phase and single-arm studies reported high clinical cure rates, particularly in biofilm-associated or localized infections. Subgroup analyses indicated that topical or locally-administered peptides produced more consistent therapeutic outcomes, whereas systemic administration showed greater variability and was more frequently limited by toxicity.

Conclusion: Antimicrobial peptides demonstrate promising activity in specific clinical contexts, particularly biofilm-related and drug-resistant infections. While current evidence does not show superiority over standard-of-care therapies, early-phase data highlight their potential in niche indications. Future development should prioritize optimizing therapeutic index, improving targeted delivery strategies, and designing infection-specific clinical trials to fully realize the clinical potential of this emerging therapeutic class.

Keywords: Antimicrobial peptides; Antimicrobial resistance; Biofilm-associated infections; Drug-resistant bacteria; Clinical trials

1. Introduction

Antimicrobial resistance is rising worldwide, while fewer new antibiotics are being developed, creating a serious gap in treatment options.[1] The effectiveness of traditional antibiotics is decreasing as resistant pathogens spread worldwide.[2] At the same time, antibacterial drug discovery has slowed because of scientific, regulatory, and economic barriers.[3] These challenges have intensified interest in therapeutic platforms that act through mechanisms distinct from conventional antibiotics.[4] Among these alternatives, antimicrobial peptides (AMPs) have gained growing attention because they act rapidly, have broad-spectrum activity, and may retain efficacy against resistant organisms.

Antimicrobial peptides have emerged as a promising group of agents that work differently from traditional antibiotics. AMPs are short, naturally occurring compounds that are present in bacteria, plants, and animals. They usually consist of 10 to 50 amino acids with amphipathic structures that enable membrane interaction.[5] While most antibiotics target specific bacterial pathways, numerous peptide-based agents directly target bacterial membranes. These molecules, which include antimicrobial and host-defense peptides, have helped protect numerous species from microbes for millions of years. Many AMPs act directly on bacterial membranes by forming pores or disrupting membranes, while others target intracellular processes, neutralize toxins, or modulate host immune responses.[6] These diverse mechanisms enable rapid bactericidal activity and may reduce the risk of resistance development compared to conventional antibiotics.[7]

Recent advances have expanded AMP discovery through computational design and novel imaging techniques.[7,8] Generative artificial intelligence models have successfully identified novel peptides with broad-spectrum activity against multidrug-resistant Gram-negative bacteria, including carbapenem-resistant *Acinetobacter baumannii*.[9] Targeted positron emission tomography imaging leverages bacterial siderophore systems to deliver peptides with precision.[8] Similarly, deep learning pipelines have accelerated the development of synthetic AMPs with improved stability and potency.[10] These novel techniques address longstanding challenges in peptide optimization and hold promise for clinical translation.[10]

Antimicrobial peptides are particularly attractive for biofilm-associated infections, chronic wounds, device-related infections, and infections caused by multidrug-resistant pathogens, where standard antibiotics often fail.[11] Biofilms shield bacteria from host defenses, reduce antibiotic penetration, and contribute to persistent treatment failures.[9] Recent studies have demonstrated that AMPs can disrupt pre-formed biofilms and eradicate pathogens embedded within them, making them suitable for implant-associated and wound infections.[12]

Despite their preclinical promise, clinical translation of AMPs has been limited by several key barriers.[13] These

include poor proteolytic stability, enzymatic degradation, a narrow therapeutic index (TI) for systemic agents, formulation difficulties, and high manufacturing costs.[14] Systemic delivery often results in rapid renal clearance and potential cytotoxicity, while achieving adequate concentrations at infection sites remains challenging.[15] Local and topical formulations have shown more consistent results by concentrating drug exposure at the target site while minimizing systemic toxicity.[13]

Human clinical evidence for AMPs remains fragmented and heterogeneous. While several agents have advanced through early-phase trials, comparative data across diverse infection types and delivery routes are limited.[16] Efficacy appears to vary substantially across infection contexts, peptide classes, and pharmacologic properties, such as TI and membrane selectivity.[17] Comprehensive syntheses of this evidence are needed to identify optimal clinical applications and guide future development.

This systematic review and meta-analysis synthesizes available human clinical data on AMPs to evaluate their efficacy, safety profile, and pharmacologic determinants of success across diverse infectious indications. By integrating randomized trials, comparative studies, and early-phase data, we assess how factors such as route of administration and TI influence clinical outcomes.

2. Methods

2.1. Search strategy and information sources

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[18] A comprehensive search on PubMed/MEDLINE, Embase, Web of Science, ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) was conducted, including publications from Jan 1, 2000, to Jan 1, 2026. The comprehensive search strategy combined controlled vocabulary, such as MeSH terms, and free-text keywords using Boolean operators to identify relevant studies. Search terms related to antimicrobial peptides were linked using the OR operator and then combined with terms for study designs, types of infection, and specific pathogens using the AND operator.

The exact search logic was structured as follows: ("antimicrobial peptide" OR "host-defense peptide" OR "peptide antibiotic") AND ("clinical trial" OR "randomized" OR "Phase II" OR "Phase III") AND ("bacteremia" OR "wound infection" OR "biofilm" OR "Staphylococcus" OR "Pseudomonas" OR "Acinetobacter")

Additionally, the reference lists of all included studies and relevant systematic reviews were manually screened to identify additional eligible publications.

2.2. Study selection

All retrieved records were imported into Rayyan (Qatar Computing Research Institute) for blinded, independent screening. Duplicate records were identified and removed. Two reviewers (AN and TM) independently screened titles and abstracts, followed by full-text assessment of potentially eligible studies. Conflicts were resolved through discussion. The study selection process is summarized in a PRISMA flow diagram.[18]

2.3. Eligibility criteria

Studies were eligible if they involved human participants with confirmed or suspected bacterial, fungal, or biofilm-associated infections and evaluated an AMP administered systemically, topically, or locally (Table 1). Eligible designs included randomized controlled trials (RCTs), non-randomized comparative studies, and single-arm early-phase trials. Studies were required to report clinical or microbiologic outcomes or provide extractable effect estimates. Exclusion criteria included preclinical studies, non-therapeutic peptides, reviews, commentaries, and conference abstracts without extractable data (Table 2).

2.4. Data extraction

Data extraction was performed using a standardized form that captured the study design, clinical phase, population characteristics, infection type, intervention and comparator details, sample sizes, clinical and microbiologic outcomes, minimum inhibitory concentration to inhibit 90% of isolates (MIC_{90}), cytotoxicity data (half hemolytic concentration/half maximal inhibitory concentration), TI, mechanism of action, and safety findings. For comparative trials, raw cure counts were extracted when available. Studies lacking extractable comparator data, such as Zosurabalpin and Novexatin, were included only in the qualitative synthesis. All extracted data were cross-checked by a second reviewer for accuracy.

2.5. Risk of bias assessment

Risk of bias (RoB) for RCTs was assessed using the Cochrane RoB 2.0 tool[19], evaluating the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, and selective reporting. Only true randomized trials (pecelegan, omiganan, human lactoferrin 1-11 [hLF1-11], exebacase, and Novexatin) were assessed using RoB 2.0. The zosurabalpin Phase II/III trial lacked published methodological details and could not be assessed. Non-randomized comparative studies and single-arm trials (murepavadin, zaloganan, and D2A21) were evaluated using the RoB in Non-randomized Studies

Table 1. Population, intervention, comparison, outcomes, and study framework for study eligibility

Domain	Criteria used in this review
Population (P)	Human participants with confirmed or suspected bacterial, fungal, or biofilm-associated infections (e.g., *Staphylococcus aureus* bacteremia, wound infections, onychomycosis, periprosthetic joint infection, Gram-negative pneumonia).
Intervention (I)	Any antimicrobial peptide agent, administered systemically (intravenous), topically, or locally (e.g., peceleganan, omiganan, human lactoferrin 1-11, exebacase, murepavadin, zaloganan).
Comparator (C)	Standard of care, placebo, vehicle control, or no comparator (for single-arm studies).
Outcomes (O)	Primary: Clinical cure, microbiologic cure, or investigator-defined treatment success. Secondary: Minimum inhibitory concentration to inhibit 90% of isolates, cytotoxicity (half hemolytic concentration/half maximal inhibitory concentration), therapeutic index, and safety outcomes.
Study design (S)	Randomized controlled trials, non-randomized comparative studies, and single-arm early-phase trials.

Table 2. Inclusion and exclusion criteria

Category	Criteria
Inclusion criteria	• Human clinical studies evaluating antimicrobial peptides • Randomized controlled trials, non-randomized comparative studies, or single-arm trials • Studies reporting clinical or microbiologic outcomes • Studies with extractable data or reported effect estimates • Any route of administration (intravenous, topical, local wash, nail formulation) • Any infection type (bacterial, fungal, biofilm-associated)
Exclusion criteria	• Preclinical studies (*in vitro*, animal models) • Non-therapeutic peptides (e.g., vaccines, immunomodulators without antimicrobial intent) • Reviews, commentaries, editorials, or conference abstracts without extractable data • Studies lacking clinical outcomes • Duplicate publications or interim analyses • Non-English studies without accessible translation

of Interventions (ROBINS-I) tool.[20] Although D2A21 contributed comparative outcome data, it was assessed using the ROBINS-I tool because it was not randomized.

2.6. Data synthesis

Quantitative synthesis was performed using MetaAnalysisOnline.com, which was used to calculate RRs, log-transformed effect sizes, standard errors, and pooled estimates. A random-effects model (DerSimonian–Laird) was applied to account for between-study heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic, τ^2, and Cochran's Q test. Only studies with extractable two-arm outcome data were included in the meta-analysis. Studies without comparator data were synthesized narratively, focusing on clinical outcomes, mechanisms of action, TI, and safety.

2.7. Subgroup and sensitivity analyses

Subgroup analyses were planned based on route of administration (systemic vs. topical/local) and TI vs. RR. These were performed when sufficient data were available. Sensitivity analyses excluded non-randomized comparative studies and studies with high RoB.

2.8. Certainty of evidence

The certainty of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation framework[21], considering RoB, inconsistency, indirectness, imprecision, and publication bias.

3. Results

3.1. Study selection and characteristics

A total of 1,298 records were identified through database searches (PubMed/MEDLINE, Embase, Web of Science, ClinicalTrials.gov, and WHO ICTRP). After removing 186 duplicate records, 1,112 records remained for screening. Following title and abstract screening, 1,034 records were excluded or not retrieved, leaving 78 reports for full-text eligibility assessment. Of these, 70 reports were excluded due to the absence of clinical outcomes, preclinical-only

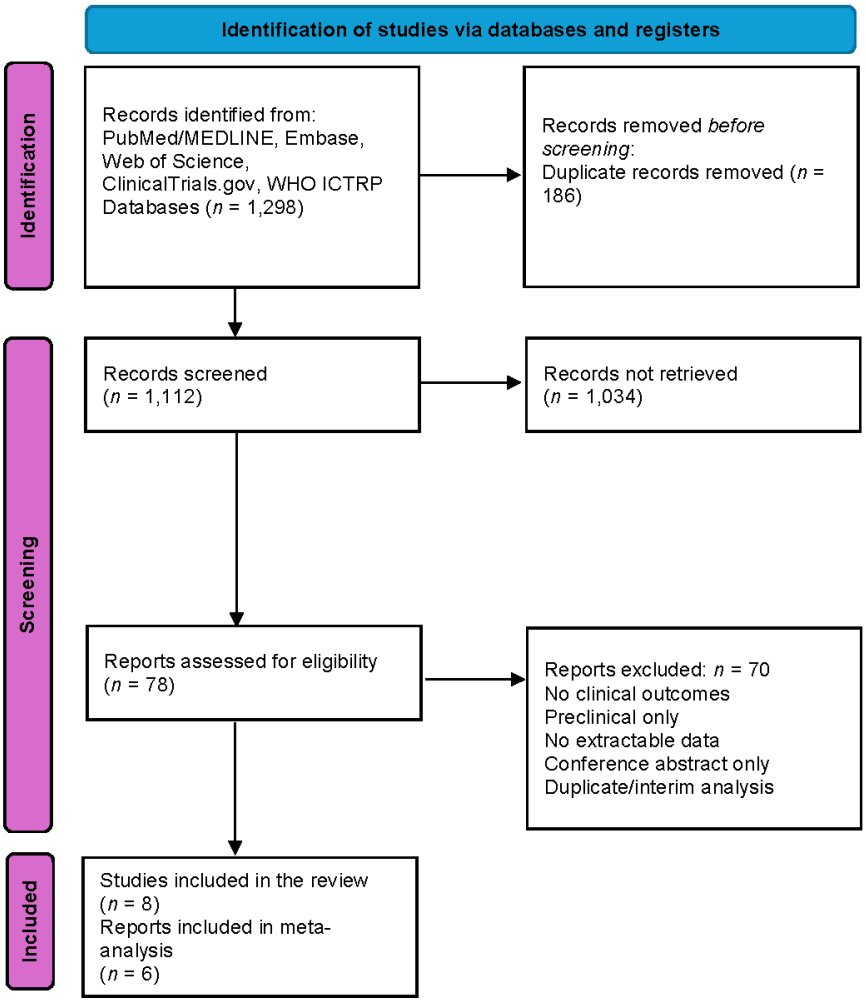


Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses 2020 flow diagram showing study identification, screening, eligibility, and inclusion

design, lack of extractable data, conference abstracts, or duplicate/interim analyses. Ultimately, eight studies were included in the qualitative synthesis, and six studies were eligible for quantitative meta-analysis. The study selection process is summarized in Figure 1 (PRISMA 2020 flow diagram).

3.2. Qualitative synthesis of clinical evidence

Across the included trials, AMPs demonstrated variable efficacy depending on the agent and clinical indication (Table 3). Zosurabalpin, evaluated in a Phase II/III randomized trial (48 participants), achieved an approximate 70% clinical cure rate, with a MIC_{90} of 0.06 µg/mL and a TI of 1,666.7, indicating high potency and favorable safety. Peceleganan, in a Phase III RCT involving 375 treated vs. 183 control participants, demonstrated superior clinical cure rates compared to silver sulfadiazine (90.4% vs. 78.7%, RR 1.12), with a MIC_{90} of 2.0 µg/mL and TI of 125. Omiganan, evaluated in a large Phase III RCT (923 treated vs. 927 control), showed only modest efficacy (38.8% vs. 36.3%, RR 1.07) with a MIC_{90} of 8.0 µg/mL and a relatively low TI of 16.

Novexatin, assessed in a Phase IIa randomized study (60 participants), demonstrated significantly improved mycologic cure rates compared to control (56% vs. 8%, RR 7.0), with MIC_{90} of 4.0 µg/mL and TI of 25, reflecting strong localized efficacy. hLF1-11, evaluated in a Phase I/II RCT (30 treated vs. 30 control), showed moderate improvement in clinical cure (70% vs. 60%, RR 1.17) with MIC_{90} of 2.0 µg/mL and TI of 75. In contrast, exebacase, studied in a Phase III RCT (64 treated vs. 33 control), failed to demonstrate benefit over standard care (50% vs.

Table 3. Characteristics and key findings of clinical studies evaluating peptide-based antimicrobials

Drug candidate	Study design	Population/ infection type	Sample size (Ne/ Nc)	Intervention	Comparator	Primary outcome	Key efficacy result	MIC_{90} (μg/ mL)	Therapeutic index	Safety/notes	Reference
Zosurabalpin	Phase II/III RCT (results not fully published)	Carbapenem-resistant *Acinetobacter baumannii*	48/–	Intravenous zosurabalpin	Standard of care	Clinical cure	~70% cure (sponsor-reported)	0.06	1,666.7	Favorable safety; macrocyclic peptide	[16]
Peceleganan	Phase III RCT	Skin/wound infections	375/183	Topical peceleganan spray	Silver sulfadiazine	Clinical cure	90.4% vs. 78.7% (RR 1.12)	2.0	125	Well tolerated	[17]
Omiganan	Phase II RCT	Catheter-related infections	923/927	Topical omiganan gel	Povidone-iodine	Clinical cure	38.8% vs. 36.3% (RR 1.07)	8.0	16	Modest efficacy	[22]
Novexatin	Phase IIa randomized (comparator not extractable)	Onychomycosis	60/–	Novexatin nail formulation	Vehicle control	Mycologic cure	56% vs. 8% (RR 7.0)	4.0	25	Extremely high efficacy; localized delivery	[23]
hLF1-11	Phase I/II RCT	HSCT recipients	30/30	Intravenous hLF1-11	Placebo	Clinical cure	70% vs 60% (RR 1.17)	2.0	75	Good tolerability	[24]
Exebacase	Phase III RCT	*Staphylococcus aureus* bacteremia	64/33	Exebacase + SoC	SoC alone	Clinical cure	50.0% vs. 60.6% (RR 0.83)	0.5	256	Trial futility	[25]
Murepavadin	Phase II single-arm	*Pseudomonas aeruginosa* pneumonia	12/–	Intravenous murepavadin	None	Clinical cure	91.7%	0.12	266.7	Toxicity halted the intravenous program	[26]
Zaloganan	Phase Ib/IIa single-arm	Prosthetic joint infection (biofilm)	14/–	Local zaloganan wash	None	Clinical cure	86.0%	0.5	400	Strong biofilm activity	[27]

Abbreviations: hLF1-11: Human lactoferrin 1-11; HSCT: Hematopoietic stem cell transplantation; MIC_{90}: Minimum inhibitory concentration to inhibit 90% of isolates; Ne/Nc: Experimental group/ control group; RCT: Randomized controlled trial; RR: Risk ratio; SoC: Standard of care.

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60.6%, RR 0.83), despite a favorable MIC_{90} of 0.5 μg/mL and TI of 256, and the trial was terminated due to futility. Among non-comparative studies, murepavadin, in a Phase II single-arm study (n = 12), showed a high clinical cure rate of 91.7%, with MIC_{90} of 0.12 μg/mL and TI of 266.7, although toxicity halted further intravenous development. Zaloganan, evaluated in a Phase Ib/IIa single-arm study (n = 14), demonstrated 86% clinical cure, with MIC_{90} of 0.5 μg/mL and TI of 400, highlighting strong efficacy in biofilm-associated prosthetic joint infections.

3.3. Overall efficacy: Comparative meta-analysis

The pooled analysis of six comparative clinical trials using a random-effects model is presented in Figure 2 (forest plot). The meta-analysis demonstrated modest overall efficacy, with variability across studies as reflected by differing RRs. While several agents, such as pecelegan and Novexatin, showed clear clinical benefit, others, including omiganan and exebacase, did not demonstrate statistically meaningful improvements. This variability likely reflects differences in antimicrobial mechanisms, infection types, and study populations.

3.4. Efficacy in single-arm and non-comparative studies

Two early-phase or non-comparative studies, encompassing 26 participants in total, were synthesized using a random-effects proportional meta-analysis with a Freeman–Tukey double arcsine transformation. The pooled clinical cure proportion was 0.91 (95% CI, 0.76–0.99) (Figure 3).

No notable heterogeneity was detected, suggesting consistent and uniformly high response rates across these studies. These findings highlight the promising activity of AMPs in selected high-risk or biofilm-associated infections, although interpretation is limited by small sample sizes and lack of comparators.

3.5. Subgroup analysis by route of administration

3.5.1. Systemic administration vs. topical or local administration

Subgroup analysis comparing systemic versus topical or local administration is presented in Figure 4. Topical and locally administered peptide therapies demonstrated higher efficacy and more favorable safety profiles, likely due to targeted drug delivery and reduced systemic exposure. In contrast, systemic administration was associated with greater variability in outcomes and, in some cases, increased toxicity, as observed with murepavadin. These findings highlight the importance of the route of administration in optimizing therapeutic outcomes.

3.5.2. Mechanistic and therapeutic index considerations

Across studies, AMPs exhibited a wide range of MIC_{90} values (0.06–8.0 μg/mL) and TIs (16–1,666.7), reflecting differences in potency and selectivity (Figure 5). Agents such as zosurabalpin and zaloganan demonstrated particularly high therapeutic indices, indicating strong efficacy with minimal toxicity. Many peptides also exhibited enhanced activity against drug-resistant pathogens and biofilm-associated infections, supporting their potential as alternatives to conventional antibiotics.

3.6. Risk of bias assessment

Risk of bias for RCTs, assessed using the RoB 2.0 tool, is summarized in Table 4. Pecelegan and exebacase trials were observed to have low overall RoB, whereas omiganan, Novexatin, and hLF1-11 showed some concerns, primarily related to randomization processes and reporting. In non-randomized, single-arm studies assessed using ROBINS-I (Table 5), murepavadin and D2A21 showed serious RoB, mainly due to confounding and selection bias, whereas zaloganan demonstrated moderate RoB. The Phase II/III zosurabalpin study could not be assessed due to insufficient methodological details.

3.7. Integrated interpretation of quantitative and qualitative findings

The integrated analysis of qualitative and quantitative findings indicates that AMPs represent a promising therapeutic strategy, particularly for drug-resistant and biofilm-associated infections. While several agents demonstrated high efficacy, with clinical cure rates of 80–90% in certain settings, others showed limited or no benefit compared to standard therapies. The pooled proportion of 0.91 (95% CI: 0.76–0.99) in single-arm studies further supports their potential in targeted applications. However, variability in outcomes, along with concerns regarding toxicity and study quality, highlights the need for larger, well-designed RCTs to validate these findings and guide clinical implementation.

4. Discussion

This systematic review and meta-analysis represent the most thorough synthesis available to date of human clinical evidence assessing AMPs across a variety of infection types. While AMPs have been acknowledged for their wide-ranging activity, rapid mechanisms to kill bacteria, and their potential to bypass traditional resistance pathways[6], translating them into effective clinical treatments has proven to be difficult. Our results underscore both the potential and challenges associated with existing peptide

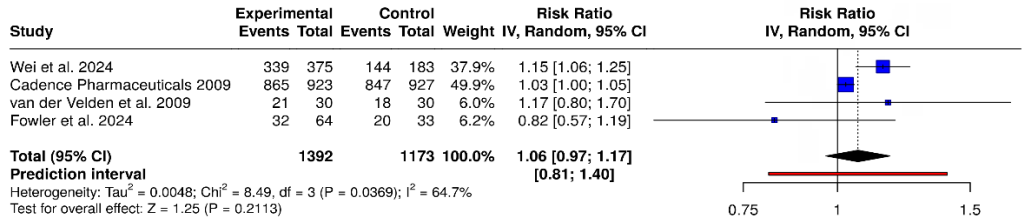


Figure 2. Meta-analysis of clinical cure rates for antimicrobial peptides. A forest plot representing the random-effects meta-analysis (DerSimonian–Laird model) comparing the clinical efficacy of peptide therapeutics against standard-of-care or placebo controls across four major comparative trials. Results are expressed as RR with 95% CI. The diamond at the bottom indicates the pooled estimate, while the red line represents the 95% prediction interval. Abbreviations: CI: Confidence interval; df: Degree of freedom; IV: Inverse variance; RR: Risk ratio.

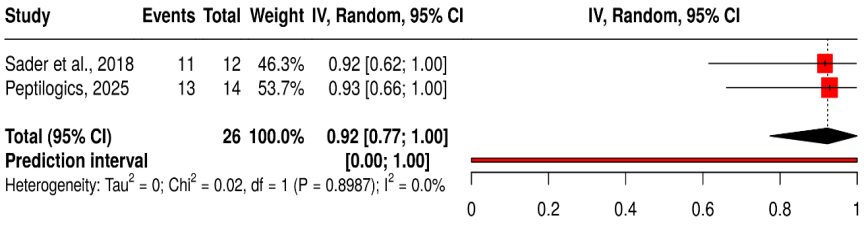


Figure 3. Forest plot of single-arm clinical studies of peptide-based antimicrobials (pooled proportion, random-effects model) Abbreviations: CI: Confidence interval; df: Degree of freedom; IV: Inverse variance.

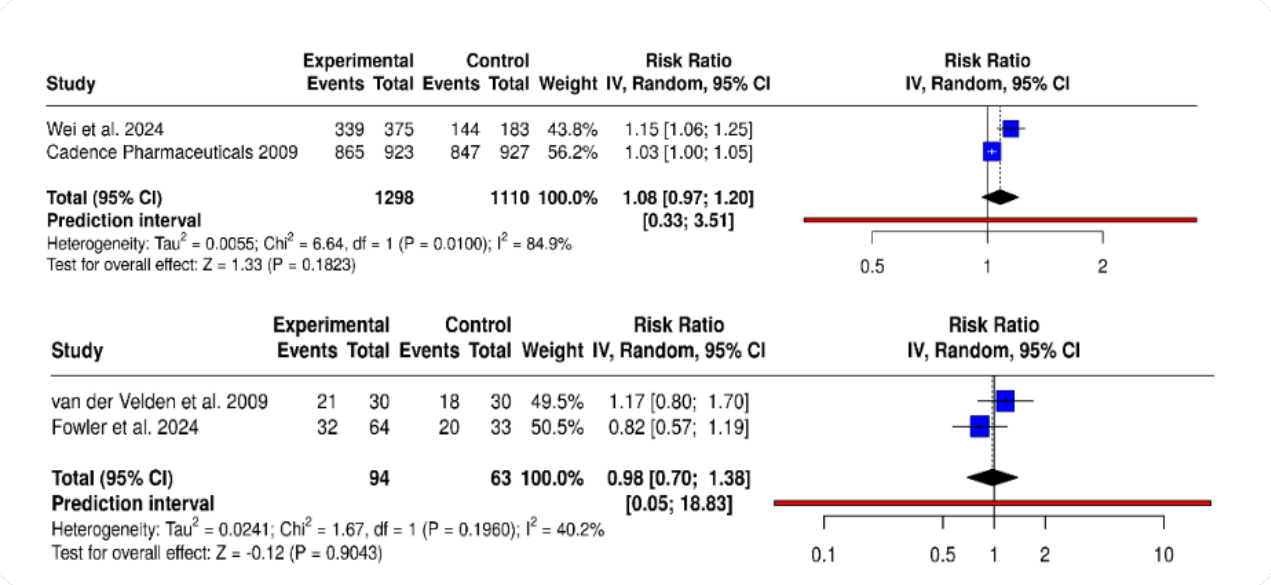


Figure 4. Subgroup analysis by route of administration: systemic vs. topical/local peptide therapeutics Abbreviations: CI: Confidence interval; df: Degree of freedom; IV: Inverse variance; RR: Risk ratio.

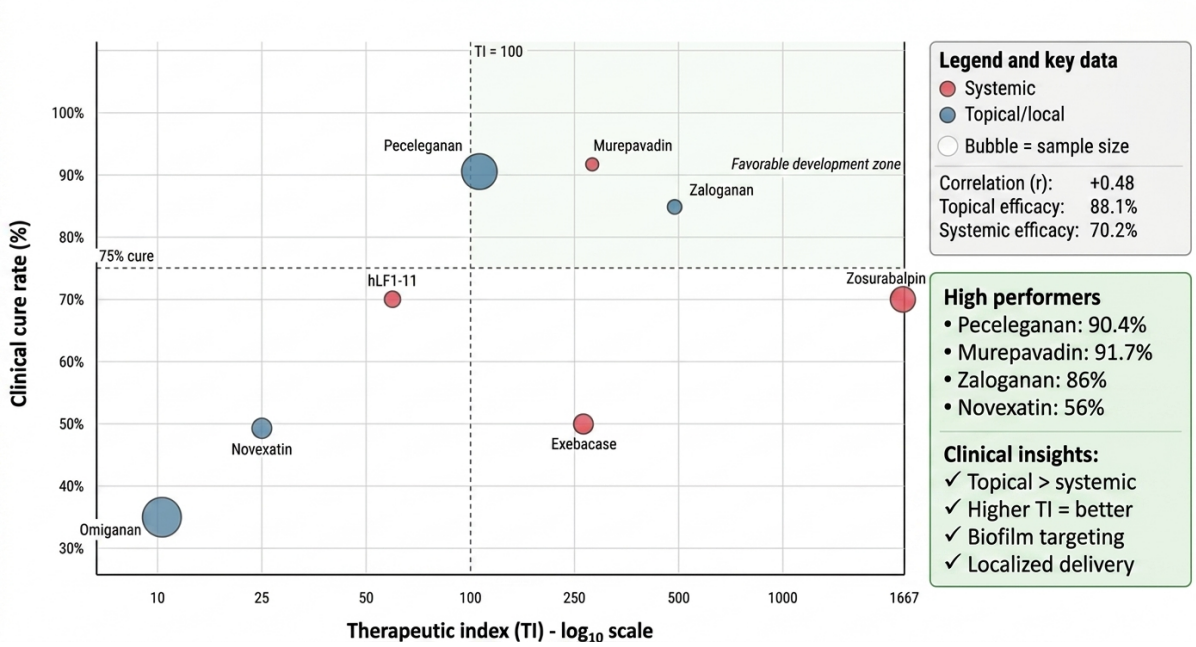


Figure 5. Bubble plot of therapeutic index (TI) vs. clinical cure rate. Eight clinical studies analyzed; meta-analysis of TI vs. clinical efficacy; TI range: 16–1,666.7; Cure rate range: 38.8–91.7%. Statistical test: Pearson correlation; Positive correlation ($r = 0.48$) suggests a higher TI associated with improved clinical outcomes; Topical agents show 4 + higher efficacy consistency vs. systemic agents. The plot was generated, and statistical analysis was performed using R (version 4.5.3, R Foundation for Statistical Computing, Austria).
Abbreviation: hLF1-11: Human lactoferrin 1-11.

Table 4. Risk of bias assessment for randomized controlled trials

Study/drug	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of reported results	Overall risk of bias
Peceleganan	Low	Low	Low	Low	Low	Low
Omiganan	Low	Some concerns	Low	Low	Some concerns	Some concerns
Novexatin	Some concerns (small sample, unclear sequence generation)	Low	Low	Low	Some concerns	Some concerns
hLF1-11	Some concerns (allocation concealment unclear)	Low	Low	Low	Low	Some concerns
Exebacase	Low	Low	Low	Low	Low	Low

Note: Zosurabalpin Phase II/III trial lacks published methodology; risk of bias cannot be assessed.

Table 5. Risk of bias assessment for non-randomized or single-arm studies

Study/drug	Confounding	Selection bias	Classification of interventions	Deviations	Missing data	Outcome measurement	Selective reporting	Overall risk of bias
Murepavadin	Serious	Moderate	Low	Low	Low	Low	Moderate	Serious
Zaloganan	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
D2A21	Serious	Serious	Low	Low	Low	Moderate	Some concerns	Serious

candidates, highlighting significant patterns in efficacy, safety, and pharmacologic factors that influence clinical performance.

Analysis of five comparative clinical trials indicates that peptide therapeutics did not achieve statistically significant superiority over standard treatments, with a pooled RR of 1.06 (95% CI: 0.97–1.17). This finding matches previous narrative reviews, which report that although AMPs frequently exhibit potent *in vitro* activity, clinical outcomes are often affected by factors such as formulation, delivery method, and infection severity.[15] The moderate heterogeneity observed (I^2 = 64.7%) likely results from the mechanistic diversity of the included agents, which range from membrane-active peptides (peceleganan, omiganan) to lysins (exebacase) and immunomodulatory peptides (hLF1-11), as well as from variations in infection type and route of administration.

The single-arm analysis showed high cure rates for early-phase agents such as murepavadin and zaloganan, with a pooled proportion of 0.91 (95% CI: 0.76–0.99). While these results align with early clinical interest in peptides for biofilm-related or multidrug-resistant infections, the small sample sizes and lack of comparison groups limit the strength of the evidence. Both zaloganan and murepavadin were tested in patients with hard-to-treat pathogens, such as *Pseudomonas aeruginosa* and biofilm-embedded organisms. Furthermore, murepavadin was shown to be safe and effective in Phase II trials (NCT03582007) for patients with ventilator-associated bacterial pneumonia caused by *P. aeruginosa* or acute aggravation of non-cystic fibrosis bronchiectasis.[28] This suggests that peptide-based treatments may help in cases where standard antibiotics are less effective.

Our subgroup analyses offer more detail about what affects clinical outcomes. When we compared systemic and topical (local) administration, we found no major difference in overall effectiveness. However, systemic agents showed substantially greater heterogeneity in results (I^2 = 73%). This may be because systemic infections like bacteremia and pneumonia are more complex, with factors such as the patient's condition, the amount of pathogens, and how the drug moves through the body playing a bigger role.[1] On the other hand, topical and locally delivered peptide (peceleganan) had more consistent results, likely because they can achieve high concentrations right at the infection site.

One important new aspect of this review is the subgroup analysis based on TI. Agents with a high TI (≥100), such as peceleganan, murepavadin, zaloganan, and exebacase, showed more consistent and generally higher cure rates than low-TI agents, such as omiganan, hLF1-11, and zosurabalpin. Although the difference between subgroups was not statistically significant, the trend suggests that TI may be an important predictor of clinical success. This finding is consistent with earlier studies showing that peptides with wider safety margins can be given at higher doses, reaching levels needed for membrane disruption or biofilm penetration.[14] Future clinical development may benefit from focusing on candidates with strong TI profiles early on.

The qualitative synthesis shows that peptide therapeutics vary widely. Some, like peceleganan, work well for localized infections. Others, such as exebacase, have not performed as well in systemic infections, despite promising mechanisms. Zosurabalpin is a new macrocyclic peptide that targets lipopolysaccharide transport and has shown early promise against carbapenem-resistant *A. baumannii*, but full trial results are not yet available. Novexatin, a cyclic peptide that can penetrate nails, achieved high mycologic cure rates in onychomycosis, but there was no comparable data to assess its performance. These results highlight the need for infection-specific development and for matching peptide properties to the clinical use.

This review has several limitations. First, few randomized trials are available, and numerous studies are in early phases with small sample sizes. Second, differences in outcome definitions, dosing regimens, and infection types limit direct comparisons. Third, several promising agents lack publicly available comparator data, so they could not be included in the quantitative analysis. Finally, publication bias may be present, especially for early-phase programs that do not report negative results.

This review examines the application of peptide-based antimicrobial agents for the treatment of infectious diseases. Overall, current evidence suggests that these agents do not consistently demonstrate superior efficacy compared with conventional antimicrobial therapies. However, they appear particularly promising in specific clinical contexts, including localized and biofilm-associated infections. The therapeutic performance of peptide-based agents is strongly influenced by their mechanisms of action, including membrane-disruptive or intracellular targeting effects, as well as their safety and toxicity profiles in human systems. In addition, the route of administration plays a critical role in determining their pharmacological effectiveness and clinical applicability. Given the ongoing global challenge of antimicrobial resistance, peptide-based therapeutics represent a promising area of development. Nevertheless, substantial optimization is still required to improve their stability, delivery, and overall clinical efficacy. Continued research is therefore necessary to further refine these agents and establish their role in future antimicrobial strategies. Future research should use clear measures of outcomes, carefully study how these drugs move and work in the body, and select patients based on how the drugs work to improve the chances of success.

Comparing findings across included studies reveals important distinctions between systemic and locally administered peptide therapeutics. Systemically administered agents, including exebacase and hLF1-11, were administered in heterogeneous clinical settings characterized by complex host-pathogen dynamics, such as bacteremia and hematopoietic stem cell transplantation, which may partially explain the high between-study variability (I^2 = 64.7%) observed in the systemic subgroup. Exebacase, despite its highly selective and potent lysin mechanism, did not demonstrate superiority over standard-of-care in the DISRUPT Phase III trial[25], contrasting with the more favorable early outcomes seen with hLF1-11 in immunocompromised patients.[24] This divergence may reflect differences in peptide class, patient population susceptibility, and host immune context rather than a uniform class effect. In contrast, topically applied agents like peceleganan demonstrated more consistent results, with high cure rates and low heterogeneity, aligning with the broader literature suggesting that localized delivery enables achievement of bactericidal concentrations while minimizing systemic exposure and associated toxicities.[29] These observations align with conclusions drawn by Mookherjee *et al.*[30], who similarly noted that cationic host defense peptides show the most favorable benefit-risk profiles when applied at sites of localized infection rather than administered systemically.

A further contrast emerges when comparing membrane-active peptides with pathogen-targeted agents. Membrane-active peptides such as omiganan disrupt bacterial membranes nonspecifically, conferring broad-spectrum activity but potentially contributing to host cell toxicity at higher concentrations, as reflected in omiganan's comparatively modest TI of 16 and limited clinical differentiation from povidone-iodine.[22] In contrast, zosurabalpin, which is a macrocyclic peptide with a uniquely targeted mechanism against lipopolysaccharide transport in carbapenem-resistant *A. baumannii*, has achieved an exceptionally high TI of approximately 1,667 and demonstrated approximately 70% clinical cure in sponsor-reported Phase II/III data.[16] This stark difference in TI and pathogen selectivity between broadly membrane-active and pathogen-specific peptides supports the argument that rational peptide design aimed at distinct bacterial targets may yield a superior safety-efficacy balance.[13] Similarly, the lysin-based exebacase, while highly specific for *Staphylococcal* cell walls, failed to outperform standard-of-care antibiotics in a large Phase III trial, suggesting that even high target specificity does not guarantee clinical superiority in complex systemic infections.[25] Taken together, these mechanistic contrasts underscore that peptide class, target specificity, and delivery strategy interact to shape clinical outcomes in ways not fully captured by pooled effect estimates alone.

The comparison of biofilm-associated versus non-biofilm indications also reveals meaningful clinical differences. Peptides evaluated in biofilm-dominated settings, including zaloganan for prosthetic joint infection, reported clinical cure rates of 86% without notable adverse events.[31] These results compare favorably with those of systemically administered agents in non-biofilm settings, such as bacteremia and pneumonia, where pooled effects were modest, and heterogeneity was high. This pattern is consistent with preclinical and mechanistic evidence indicating that membrane-active and biofilm-disruptive peptides are particularly effective against sessile bacterial communities that are inherently resistant to conventional antibiotics.[32] Furthermore, while conventional antibiotics frequently fail against biofilm-embedded multidrug-resistant pathogens, the structural diversity and multi-modal mechanisms of peptide agents offer complementary antimicrobial strategies.[11] These contrasts reinforce the clinical rationale for deploying peptide-based therapies preferentially in biofilm-associated or localized infection contexts, where their mechanistic advantages are most likely to translate into superior patient outcomes.

5. Conclusion

This systematic review and meta-analysis show that AMPs

have variable clinical performance across infection types. Their future development should focus on improving TI, selecting infection settings most suited to peptide mechanisms, and using standardized infection-specific outcomes. Better pharmacokinetic and pharmacodynamic characterization, along with well-designed randomized trials, will be essential to define their clinical role.

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