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Comparative In Vitro Evaluation of LL-37 and Standard Antibiotics against Escherichia coli Isolates from Urinary Tract Infections: A Sustainable Healthcare Perspective

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ABSTRACT

Objective: *This study aimed to evaluates the in vitro antibacterial activity of the human cathelicidin peptide LL-37 towards E. coli which isolated from UTI patients, as well as to compare its effect with the common antibiotics like amoxicillin-clavulanic acid (AMC), aztreonam (ATM), and ceftriaxone (CRO).* ***Method:*** *In well diffusion test, LL-37 showed a clear inhibition zone, revealing strong antimicrobial activity. The time-kill assay also authorized its bactericidal action, showing a ≥3 log_{10} CFU/mL reduction within few hours and almost complete killing after 24 hours.* ***Results:*** *The mean zone diameter for LL-37 (18.4 ± 1.7 mm) was obviously greater than AMC (13.2 ± 2.1 mm) ($p < 0.01$) and higher than ATM (16.1 ± 1.9 mm), although the difference with ATM was not significant ($p > 0.05$). CRO confirmed smaller zone (14.3 ± 1.8 mm), which kind of highlight the stronger effect of LL-37.* ***Novelty:*** *The results generally supports the idea that LL-37 could be a promising alternative antimicrobial agent, showing strong activity than some of the usual antibiotics against E. coli. Its possible role in treating drug-resistant UTIs still need more studying, especially now when resistance to β-lactam antibiotics keeps increasing.*

INTRODUCTION

Urinary Tract Infections (UTIs) occur many around the world, especially in women, older people, and patient who have catheters or other health problems [1]. Escherichia coli is main bacteria behind most cases, causing around 80–90% of the uncomplicated UTIs [2]. These infections are usually cured with β-lactam antibiotics such as ampicillin and ceftriaxone, or sometimes with monobactams such as aztreonam [3,4]. However, multidrug-resistant (MDR) E. coli is growing, making these antibiotics less efficient, causing treatment failure and great costs of healthcare.

Antimicrobial Peptides (AMPs) are promising new agents [5,6]. These natural peptides are part of the innate immune system in humans and other organisms, and they attack pathogens in ways different from traditional antibiotics [7,8].

LL-37, the only human cathelicidin peptide, is identified for its broad-spectrum antimicrobial activity, mainly against for both Gram-positive and Gram-negative bacteria, with drug-resistant strains [9,10]. LL-37 not only disrupts bacterial membranes but also considers as a key role in modulating immune responses and preventing biofilm formation, a vital reason in chronic and recurrent UTIs [11].

Although the antimicrobial potential of LL-37 is already well-documented, studies specifically focus on multidrug-resistant *E. coli* isolated from urinary tract infections remain limited [12]. Furthermore, very few investigations have employed time-kill

kinetics assays, which are crucial to demonstrate the dynamic bactericidal activity of LL-37 over time [13]. These aspects provide a unique contribution to the novelty of the present work.

This study aims to assess the in *vitro* antimicrobial activity of LL-37 against clinical *E. coli* isolations obtained from patients with UTIs. Additionally, the peptide's effectiveness will be compared with that of three commonly used antibiotics, ampicillin, aztreonam and ceftriaxone. In addition to checking the inhibition zones and doing the minimum inhibitory concentration (MIC) tests, a time-kill assay was also used to examine how LL-37 kills the bacteria over time. By measuring MIC values and inhibition zones, this study tried to see how good LL-37 could be as a long-lasting and effective alternative to the usual antibiotics, especially now when antibiotic resistance keeps increasing.

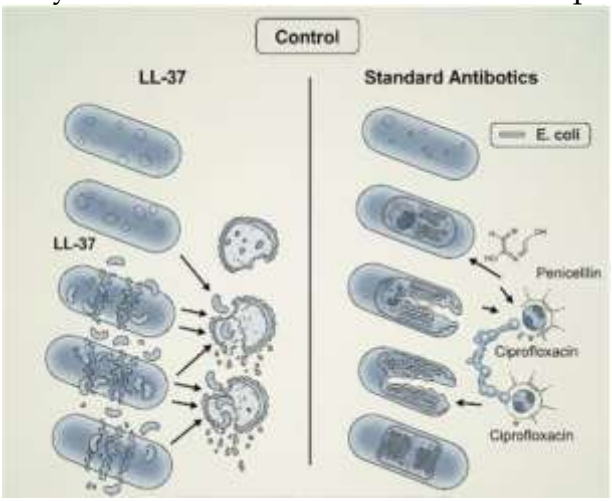

Figure 1. Comparing the effects of LL-37 and standard antibiotics on E. coli cell structure. This figure was made using Microsoft PowerPoint (Version 2019).

METHODOLOGY

Bacterial Isolates

Clinical *E. coli* specimens was taken from patients with UTIs at Al-Diwaniyah General Hospital. Each isolate was obtained from urine sample. Then, specimens were streaked onto MacConkey agar and blood agar, following with incubated aerobically at 37 °C for nearly 24 hours. Identification of *E. coli* relied on indole production, citrate utilization, and lactose fermentation. For further confirmed by using the VITEK 2 Compact system [14].

Antibiotic sensitivity examining was achieved for all isolates, including screening for ESBL activity. This examinations followed the standard CLSI phenotypic procedure [15]. Determining the resistance shapes allow us to better evaluate the activity of LL-37 against isolates to showing different levels of antimicrobial resistance.

Antimicrobial Agents

The AMP LL-37 (≥95% purity) was purchased from GenScript (USA) and reconstituted in sterile water to make the stock solution. Three common antibiotics—amoxicillin-clavulanic acid (AMC), aztreonam (ATM), and ceftriaxone (CRO)—were also used at 30 µg/mL and obtained from Sigma-Aldrich (USA). They were prepared according to the manufacturer's instructions [16]. All drugs were tested at 30 µg/mL in the diffusion test, and LL-37 was about ~6.7 µM.

Antimicrobial Susceptibility Test

The antimicrobial activity of LL-37, AMC, ATM, and CRO was tested in vitro by agar well diffusion and broth microdilution. The work followed CLSI guidelines [17]. For the agar well test, Mueller–Hinton agar plates were seeded with a bacterial suspension set to 0.5 McFarland. Small wells (6 mm) were made in the agar, and 100 µL of each drug was put inside each well. LL-37 and all three antibiotics (AMC, ATM, CRO) were tested at 30 µg/mL, with LL-37 corresponding to ~6.7 µM. Plates were incubated at 37 °C for 24 hours, after which the diameters of the inhibition zones were measured in millimeters. Each experiment was carried out in triplicate to confirm reproducibility.

The MIC of LL-37 was checked by the broth microdilution method. Two-fold dilutions were made from 1 to 128 µg/mL in 96-well plates. Each well got a standard bacterial mix and was kept at 37 °C for about 18–24 hours. The MIC was the lowest LL-37 level that stopped any visible growth [13].

Time-Kill Assay

Time-kill assay was done to check the killing effect of LL-37. *E. coli* cultures (~1×10^6 CFU/mL) were treated with LL-37 at 1× MIC (16 µg/mL) and with AMC, ATM, CRO at their MICs in Mueller-Hinton broth. The mix was kept at 37°C. Samples were taken at 0, 2, 4, 6, and 24 hours, diluted, and plated on nutrient agar. After 24 hours, CFUs were counted. A drop of ≥ 3 $\log_{10}$ CFU/mL from the start was counted as bactericidal [18].

Statistical Analysis

All tests were done in triplicate to check reproducibility. Data was analyzed using GraphPad Prism 10. Results are shown as mean ± SD. Differences in antimicrobial activity among LL-37, AMC, ATM, and CRO were evaluated by one-way ANOVA, with significance defined at p-value of < 0.05.

RESULTS AND DISCUSSION

A total of 150 clinical isolates of *E. coli* were tested for susceptibility to the antimicrobial peptide LL-37 (30 µg/mL, ~6.7 µM**7** for diffusion assays; 16 µg/mL for MIC/time-kill assays) and compared with three standard antibiotics (AMC, ATM, and CRO), 30 µg/mL for diffusion assays and at MICs for time-kill assays). Antimicrobial activity was evaluated using the agar well diffusion method and the broth microdilution method to determine the minimum inhibitory concentration (MIC) for all agents.

Antibiotic Susceptibility Testing

In the well diffusion method, LL-37 exhibited clear zones of inhibition against all tested *E. coli* isolates. The mean inhibition zone diameter for LL-37 was 18.4 ± 1.7 mm, which was remarkably greater than that of AMC (13.2 ± 2.1 mm) and CRO (14.3 ± 1.8 mm). ATM showed a mean zone of 16.1 ± 1.9 mm, which was closer to LL-37 in performance. LL-37 showed a significantly larger inhibition zone than AMC ($p < 0.01$) and an even larger one than CRO ($p < 0.05$). Its zone was bigger than ATM, but the difference was not significant ($p > 0.05$). Table 1 summarizes inhibition zones, MIC ranges, MIC_{50}, MIC_{90}, and statistical results. Figure 2 shows LL-37 (central well) compared with AMC, ATM, and CRO (30 µg/mL each). LL-37 had the biggest and most uniform zone, showing its strong activity [19].

Among 150 *E. coli* isolates, 45% were resistant: 23.3% ESBL-positive, 22% MDR, and 55% non-ESBL. LL-37 inhibited all groups. Mean zones were 21.0 ± 2.1 mm for non-ESBL, 18.4 ± 2.2 mm for ESBL, and 15.9 ± 2.4 mm for MDR (Table 1). This shows LL-37 keeps activity even against strains with ESBL or multidrug resistance. Overall, the data support

LL-37 as a promising alternative or adjunctive agent for the treatment of urinary tract infections caused by both susceptible and resistant *E. coli* isolates.

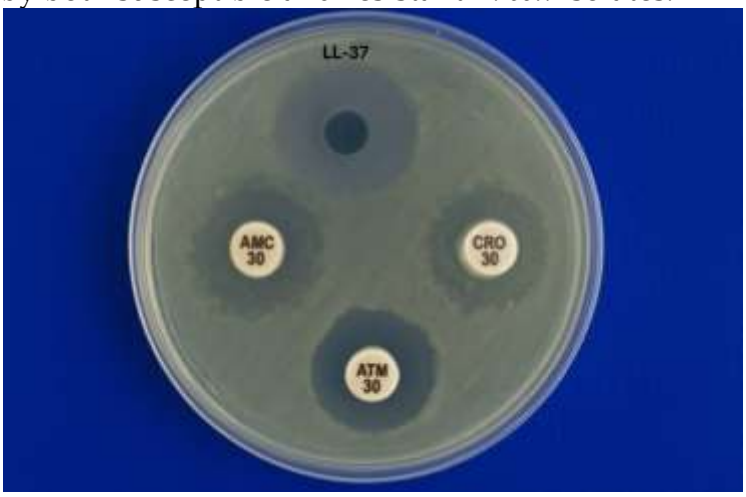

Figure 2. Antibacterial activity of LL-37 (30 µg/mL; ~6.7 µM) compared with standard antibiotics AMC (amoxicillin-clavulanic acid, 30 µg/mL), ATM (aztreonam, 30 µg/mL), and CRO (ceftriaxone, 30 µg/mL) using the agar well diffusion method on Mueller–Hinton agar against E. coli Isolates

Table 1. Summary of LL-37 antibacterial activity against *E. coli* isolates grouped by resistance profile

Resistance profile	No. of isolates (n=150)	Percentage (%)	Mean LL-37 inhibition zone (mm) ± SD	Range (mm)
Non-ESBL	82	54.7	21.0 ± 2.1	18–24
ESBL-positive	35	23.3	18.4 ± 2.2	15–22
MDR (≥3 drug classes)	33	22.0	15.9 ± 2.4	13–19

Minimum inhibitory concentration (MIC)

MIC values obtained by broth microdilution supported the diffusion assay findings. LL-37 showed low MICs (4–32 µg/mL, average 16 µg/mL), whereas amoxicillin-clavulanic acid had higher MICs (64 to >128 µg/mL), indicating reduced sensitivity. Aztreonam ranged from 16–64 µg/mL (average 32 µg/mL), and ceftriaxone from 32–128 µg/mL (average 48 µg/mL). One-way ANOVA revealed significant differences between LL-37 and the other antibiotics ($p < 0.05$) *Table 2.* Although LL-37's activity was similar to aztreonam, its inhibition was significantly higher than ceftriaxone ($p < 0.05$), reflecting a broader and more consistent antibacterial profile. This results agree with resent reports which showing LL-37 works against Gram-negative bacteria resistant to β-lactams [20,21]. It could overcome common resistanse mechanisms. Overall, LL-37 maybe could avoid resistanse mechanisms like β-lactamase production and changes in penicillin-binding proteins. This kind of features can aid to using it as an alternative or additional antimicrobial agent [22,23].

Table 2. Antimicrobial activity of LL-37, AMC, ATM, and CRO against 150 *E. coli* isolates (n = 150)

Agent	Zone of Inhibition *(mm)*Mean ± SD	MIC Range *(µg/mL)*	MIC_{50} / MIC_{90} (µg/mL)	Statistical Significance
LL-37	18.4 ± 1.7	4 – 32	16 / 32	[15,16]
Amoxicillin-clavulanic acid (AMC)	13.2 ± 2.1	64 – 128	128 / >128	$p < 0.01$
Aztreonam (ATM)	16.1 ± 1.9	16 – 64	32 / 64	Not significant ($p > 0.05$)
Ceftriaxone (CRO)	14.3 ± 1.8	32 – 128	64 / 128	*$p < 0.05$*

Antibiotic Susceptibility Testing

Figure 2 show the antibacterial activity of LL-37 (center well, 30 µg/mL, ~6.7 µM) compared to AMC, ATM, and CRO (30 µg each) using the agar well diffusion method on Mueller-Hinton agar. The bacterial susceptibility were shown by clear zones which formed around each well. Interestingly, LL-37 produced distinct and uniform zone, which reveal strong action against *E. coli* from UTIs. At 30 µg/mL, LL-37 gave zones equal or bigger than AMC, ATM, and CRO. This agree with other studies that LL-37 interrupt bacterial membranes and can overcomes resistance mechanisms like β-lactamase and altered penicillin-binding proteins [16,24–26]. These results suggest LL-37 could be used as alternative or extra therapy for multidrug-resistant *E. coli* in UTIs [27].

Time-Kill Assay

Time-kill assay was carried out to examine the activity of LL-37 (16 µg/mL, 1× MIC) can kill *E. coli* rapidly. LL-37 caused a ≥3 $\log_{10}$ CFU/mL drop during 6 hours, that mean it kills fast via disrupting bacterial membranes and getting around resistance like β-lactamase and altere penicillin-binding proteins [28,29]. No regrowth was observed at 24 hours, confirming lasting effect.

In contrast, AMC, ATM, and CRO acted slower than the activity of LL-37 and cannot reach a ≥3 $\log_{10}$ reduction in the same time. *Table 3* and *Figure 3* show $\log_{10}$ CFU/mL at different times. LL-37 completely cleared the bacteria by 24h, while ATM and CRO were mostly bacteriostatic. These finding agree with previous studies that LL-37 kills faster and more effective than standard antibiotics [18,30–32]. The sustained effect suggest that LL-37 could be the best choise for treating multidrug-resistant *E. coli*.

Table 3. Time-Kill Assay of LL-37 vs Standard Antibiotics Against *E. coli*

Time (h)	Control (no drug)	LL-37 (10 µg/mL)	AMC (20 µg/mL)	ATM (30 µg/mL)	CRO (30 µg/mL)	Statistical Significance
0	6.00	6.00	6.00	6.00	6.00	[16,17].
2	6.30	5.72	5.53	5.93	5.88	NS ($p > 0.05$)
4	6.49	4.90	4.08	5.79	5.68	$p < 0.05$ (LL-37, AMC vs control)
6	6.65	3.18	2.70	5.60	5.50	$p < 0.01$ (LL-37, AMC vs control)
24	>7.00	ND	ND	5.18	4.99	$p < 0.001$ (LL-37, AMC vs control)

ND: Not detectable (no colony-forming units observed)
AMC: Amoxicillin-clavulanic acid, ATM: Aztreonam, CRO: Ceftriaxone

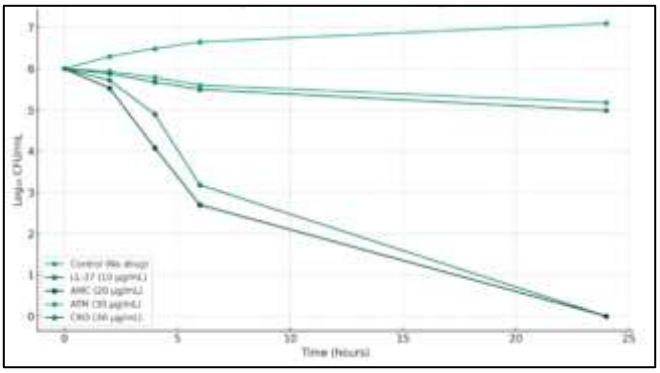

Figure 3. Time-Kill Kinetics of LL-37 Compared to Standard Antibiotics Against E. coli

Mechanism and Clinical Relevance

Unlike normal β-lactams, LL-37 (30 µg/mL in diffusion, 16 µg/mL in MIC/time-kill) kill bacteria by destroying their membranes and serving the innate immun responses [33]. This aid to evade common resistanse mechanisms. Its activity is similar to aztreonam, which is used for hard Gram-negative infections, this feature show could work against multidrug-resistant bacteria [13]. The biological role of LL-37 is naturally generated in urinary tract during infection, showing its importance [11,30]. It can also be utilized with standard antibiotics, boosting their effect and maybe reducing the dose needed [34,35]. Generaly, LL-37 could be new treatment for UTI-associated *E. coli*, in line with research on synthetic or recombinant LL-37 [36,37].

Statistical Validation

All test were done in triplicate and described as mean ± SD for reproducibility. One-way ANOVA proved LL-37 acted superior against *E. coli* than AMC, ATM, and CRO ($p < 0.05$). Time-kill result show LL-37 and AMC significantly reduced bacterial counts at 6 h and 24 h compared to control and the other antibiotics ($p < 0.01$ to <0.001), indicating ongoing and rapid killing [38,39].

CONCLUSION

Fundamental Finding: This study show that LL-37 work against E. coli from UTIs. Compared to AMC, ATM, and CRO, LL-37 gave higher and clearer inhibition zone. Time-kill assessment show a ≥3 $\log_{10}$ drop within 6 hours and complete clearance by 24 hours, that confirm LL-37 is more appropriate than standard antibiotics. **Implication:** This suggest that LL-37 could be long-lasting alternative or used together with other drugs for infections with β-lactam-resistant bacteria. Its action works by breaking bacterial membranes and can also helping the immune system. This make LL-37 different from usual antibiotics and could be promising option for future treatments of UTIs and other bacterial infections. **Limitation:** One limitation of the study is all experiments were done in vitro, so there is no laberatory animal was used to confirm the effect of LL-37 on E. coli infections. Another limitation is the small samples that gathered which maybe limits the general results. **Future Research:** Future studies should test LL-37 in animal models of urinary tract infection, like mice, to check its effectiveness, safety, and pharmacokinetics in vivo. It is also important to study the best dose, the best way to deliver it, possible synergy with standard antibiotics, and any toxicity. This kind of work will help support LL-37 as alternative or added therapy for antibiotic-resistant infections.

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