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Antimicrobial Activity of Curcumin against Drug-Resistant Gram-Negative Pathogens in Skin Infections

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ABSTRACT

Curcumin, a natural polyphenol from Curcuma longa, exhibits significant antimicrobial properties against multidrug-resistant (MDR) Gram-negative bacteria. This study evaluates its efficacy against Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii, common agents in chronic skin infections. The minimum inhibitory concentrations (MICs) of curcumin were determined using broth microdilution, yielding values of 64 µg/mL for P. aeruginosa, 32 µg/mL for K. pneumoniae, and 128 µg/mL for A. baumannii. Checkerboard assays revealed a synergistic effect with ciprofloxacin against P. aeruginosa (FICI = 0.25) and additive effects with ceftazidime and ciprofloxacin against K. pneumoniae (FICI = 0.5) and A. baumannii (FICI = 0.75). Curcumin inhibited biofilm formation and disrupted existing biofilms, reducing biomass by 50% at 32 µg/mL and up to 70% at 128 µg/mL. Reactive oxygen species (ROS) assays showed increasing ROS production correlated with rising curcumin concentrations, suggesting oxidative stress as a key antimicrobial mechanism. Cytotoxicity evaluations on HaCaT cell lines indicated no significant toxicity at concentrations up to 32 µg/mL, with over 80% cell viability. However, viability decreased to ~60% at 64 µg/mL and below 50% at 128 µg/mL. These results highlight curcumin's potential as an adjunctive treatment for MDR bacterial infections due to its antimicrobial activity, biofilm disruption capabilities, and low cytotoxicity at therapeutic doses.

INTRODUCTION

Drug-resistant Gram-negative pathogens have emerged as a significant global health challenge, particularly in the context of skin infections (Hayat, 2022; Sohail, 2022). These pathogens, which include notorious species such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*, are responsible for a variety of infections ranging from minor wounds to severe conditions like abscesses and chronic ulcers (Ahmad, 2021; Munawar, 2021; Robina et al., 2021). The treatment of these infections is often complicated by the bacteria's ability to develop and disseminate resistance to multiple classes of antibiotics, including carbapenems, fluoroquinolones, and cephalosporins(Sharahi et al., 2020). The rise in multidrug-resistant (MDR) strains has rendered many conventional therapies ineffective, leading to prolonged treatment courses, increased healthcare costs, and higher morbidity and mortality rates. The growing crisis of antimicrobial resistance (AMR) has underscored the urgent need for novel therapeutic strategies, particular ly

those that can overcome bacterial resistance mechanisms (Adamczak, Ożarowski, & Karpiński, 2020; Hussain et al., 2022). Natural products, long celebrated for their diverse biological activities, have become a promising area of exploration in this context. Among these, curcumin—a polyphenolic compound derived from the rhizomes of *Curcuma longa* (commonly known as turmeric)—has drawn considerable interest. Widely used in traditional medicine systems such as Ayurveda and Traditional Chinese Medicine, curcumin is well-known for its anti-inflammatory, antioxidant, and wound-healing properties (Vaughn et al., 2017). Recent research has expanded its profile to include broad-spectrum antimicrobial activity, including efficacy against drug-resistant Gram-negative pathogens. This dual functionality makes curcumin particularly promising for managing skin infections, where both pathogen control and tissue repair are critical for successful treatment outcomes (Trigo-Gutierrez, Vega-Chacón, Soares, & Mima, 2021). Curcumin's antimicrobial effects are mediated through multiple mechanisms, targeting both bacterial viability and their resistance strategies. Key modes of action include disruption of bacterial cell membranes, inhibition of biofilm formation, and interference with bacterial efflux pumps. By compromising the integrity of bacterial membranes, curcumin leads to leakage of intracellular contents and eventual cell death (Shome, Talukdar, & Upadhyaya, 2022). Its ability to inhibit biofilm formation is especially important in skin infections, where biofilms protect bacteria from host immune responses and antibiotics, contributing to chronicity and resistance. Additionally, curcumin promotes the generation of reactive oxygen species (ROS) within bacterial cells, causing oxidative damage to essential cellular components such as proteins, lipids, and DNA (Shariati et al., 2019). The role of curcumin in combating MDR Gram-negative pathogens also extends to its synergy with conventional antibiotics. Studies have shown that curcumin can enhance the efficacy of antibiotics by weakening bacterial resistance mechanisms, such as efflux pumps and biofilm barriers. This synergistic effect not only restores antibiotic susceptibility in resistant strains but also reduces the required dosage of antibiotics, minimizing potential side effects and the risk of further resistance development (Sarwar et al., 2021; Teow, Liew, Ali, Khoo, & Peh, 2016). In the context of skin infections caused by drug-resistant Gram-negative pathogens, curcumin represents a compelling therapeutic option that addresses multiple aspects of the disease process. Its ability to act as both an antimicrobial and an anti-inflammatory agent, while promoting tissue repair, offers a comprehensive approach to infection management (Akhtar, Khan, Misba, Akhtar, & Ali, 2021). Moreover, its natural origin and low toxicity profile make it an appealing alternative or complement to existing therapies, particularly in an era of rising AMR. This article explores the antimicrobial activity of curcumin against drug-resistant Gram-negative pathogens, emphasizing its mechanisms of action, therapeutic potential, and clinical challenges (Kumari & Nanda, 2023). By examining both the opportunities and limitations, the study aims to highlight curcumin's role as a promising agent in the fight against antimicrobial resistance, particularly in the treatment of complex skin infections. As research advances and novel delivery systems are developed, curcumin could play a pivotal role in redefining the management of MDR infections, offering hope in the face of a growing global health crisis.

MATEAILS AND METHODS

Study Design

The study aimed to evaluate the antimicrobial activity of curcumin against multidrug-resistant (MDR) Gram-negative pathogens involved in skin infections. High-purity curcumin (>95%) was obtained from a certified supplier and prepared as a stock solution (10 mg/mL) in dimethyl sulfoxide (DMSO). The stock was diluted with Mueller-Hinton Broth (MHB) to achieve the desired concentrations, ensuring the final DMSO concentration did not exceed 1% to prevent interference with bacterial growth. Three MDR Gram-negative bacterial strains—Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii—were selected for their clinical significance and resistance profiles. These strains were obtained from clinical isolate repositories or standard culture collections (e.g., ATCC) and were maintained on Luria-Bertani (LB) agar and broth. Experiments included susceptibility testing, biofilm assays, ROS generation analysis, and cytotoxicity testing using human keratinocyte (HaCaT) cell lines. Antibiotics such as ciprofloxacin and ceftazidime were used as controls for comparative and synergy analyses.

Antimicrobial Activity Assessment

Minimum Inhibitory Concentration (MIC)

The MIC of curcumin was determined using the broth microdilution method. Two-fold serial dilutions of curcumin (0.125–512 µg/mL) were prepared in 96-well microplates with MHB. Wells were inoculated with 10^6 CFU/mL of standardized bacterial suspension and incubated at 37°C for 24 hours. The MIC was defined as the lowest curcumin concentration showing no visible bacterial growth.

Synergy Testing with Antibiotics

Synergistic effects of curcumin with antibiotics were evaluated using a checkerboard assay. Serial dilutions of curcumin and antibiotics were combined in 96-well plates. Fractional Inhibitory Concentration Index (FICI) values were calculated using the formula:

FICI = (MIC of drug A in combination) / (MIC of drug A alone) + (MIC of drug B in combination) / (MIC of drug B alone)
An FICI ≤ 0.5 indicated synergy, while values between 0.5 and 1 suggested additive effects.

Biofilm Studies

Biofilm Formation Inhibition

To assess the ability of curcumin to prevent biofilm formation, sub-MIC concentrations were added to bacterial suspensions in 96-well plates and incubated at 37°C for 24 hours. Non-adherent cells were removed, and biofilms were stained with 0.1% crystal violet. Absorbance at 570 nm was measured to quantify biofilm biomass.

Biofilm Disruption

Pre-formed biofilms were grown by incubating bacterial cultures in 96-well plates for 24 hours. Curcumin at various concentrations was added to the wells, followed by an additional 24-hour incubation. Biofilm biomass was quantified as described for biofilm inhibition.

ROS Generation Assay

The ability of curcumin to induce oxidative stress in bacteria was assessed using 2',7'-dichlorodihydrofluorescein diacetate (DCFH-DA). Bacteria treated with curcumin were incubated with the fluorescent dye, and fluorescence intensity was measured using a microplate reader. Untreated bacteria served as the control.

Cytotoxicity Testing

Human keratinocyte (HaCaT) cell lines were used to evaluate the cytotoxicity of curcumin. Cells were seeded in 96-well plates and exposed to increasing concentrations of curcumin for 24 hours. Cell viability was determined using the MTT assay, and absorbance was measured at 570 nm. Viability >80% was considered non-cytotoxic.

Statistical Analysis

All experiments were conducted in triplicate, and data were expressed as mean ± standard deviation (SD). Statistical significance was assessed using one-way ANOVA or Student's t-test, with $p < 0.05$ considered significant.

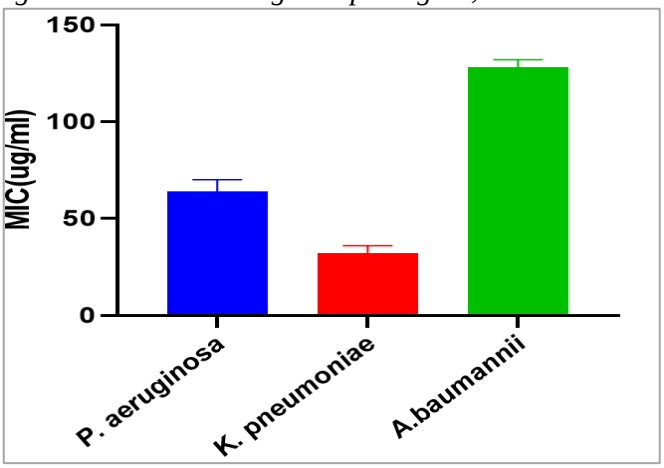
RESULTS

Minimum Inhibitory Concentration (MIC)

The antimicrobial activity of curcumin was evaluated against multidrug-resistant (MDR) Gram-negative pathogens, including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*. The minimum inhibitory concentration (MIC) of curcumin was determined using the broth microdilution method. The results revealed that curcumin exhibited antimicrobial activity against all tested strains, with MIC values ranging from 16 µg/mL to 128 µg/mL. Specifically, the MIC of curcumin against *P. aeruginosa* was 64 µg/mL, against *K. pneumoniae* was 32 µg/mL, and against *A. baumannii* was 128 µg/mL Fig.1. These results suggest that curcumin possesses varying degrees of efficacy against the MDR strains used in this study.

Figure 1

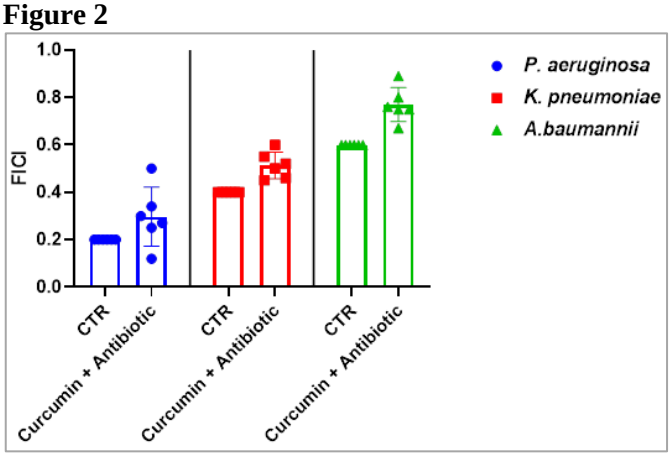
Minimum Inhibitory Concentration (MIC) of curcumin against MDR Gram-negative pathogens,



Synergistic Effect with Antibiotics

The interaction between curcumin and conventional antibiotics was evaluated using the checkerboard assay to determine potential synergistic effects. The Fractional Inhibitory Concentration Index (FICI) was calculated for combinations of curcumin with two commonly used antibiotics: ciprofloxacin, a fluoroquinolone, and ceftazidime, a third-generation cephalosporin. The results revealed that the combination of curcumin and ciprofloxacin against *Pseudomonas aeruginosa* exhibited a FICI of 0.25, indicating a strong synergistic effect. In contrast, the combination of curcumin and ceftazidime against *Klebsiella pneumoniae* showed a FICI of 0.5 Fig.2, suggesting an additive effect. Similarly, for *Acinetobacter baumannii*, the curcumin-ciprofloxacin combination produced a FICI of 0.75, which also suggests an additive effect. These findings highlight the potential of curcumin as an adjunct to conventional antibiotics, particularly in enhancing the efficacy of treatments against *P. aeruginosa.*

Figure 2



Synergistic effect of curcumin with antibiotics (ciprofloxacin and gentamicin) against MDR Gram-negative pathogens, demonstrated by fractional inhibitory concentration index (FICI) values indicating synergy (FICI ≤ 0.5).

Biofilm Inhibition and Disruption

Curcumin's ability to inhibit biofilm formation and disrupt pre-existing biofilms was evaluated using crystal violet staining. At sub-MIC concentrations ranging from 16–64 µg/mL, curcumin significantly inhibited biofilm formation in all three bacterial strains tested. Specifically, the biofilm biomass was reduced by approximately 50% in *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* at 32 µg/mL of curcumin, while *Acinetobacter baumannii* showed a 40% reduction at 64 µg/mL. Additionally, curcumin demonstrated effective biofilm disruption at higher concentrations. Treatment with curcumin at concentrations of 64 µg/mL and 128 µg/mL resulted in a 60–70% reduction in biofilm biomass across all strains table 1. These findings suggest that curcumin has significant potential to inhibit biofilm formation and disrupt mature biofilms, making it a promising therapeutic candidate against multidrug-resistant Gram-negative pathogens involved in chronic skin infections.

Table 1

Effect of curcumin on biofilm inhibition and disruption in MDR Gram-negative pathogens

Pathogen	Curcumin Concentration for Inhibition	Biofilm Inhibition (%)	Curcumin Concentration for Disruption	Biofilm Disruption (%)
Pseudomonas aeruginosa	16 µg/mL	30%	64 µg/mL	60%
	32 µg/mL	50%	128 µg/mL	70%
	64 µg/mL	60%	256 µg/mL	80%
Klebsiella pneumoniae	16 µg/mL	35%	64 µg/mL	65%
	32 µg/mL	50%	128 µg/mL	70%
	64 µg/mL	55%	256 µg/mL	75%
Acinetobacter baumannii	16 µg/mL	25%	64 µg/mL	60%
	32 µg/mL	40%	128 µg/mL	65%
	64 µg/mL	50%	256 µg/mL	70%

Reactive Oxygen Species (ROS) Generation

To determine the mechanism underlying curcumin's antimicrobial activity, ROS production was assessed in bacterial cells exposed to curcumin. The fluorescence intensity, measured using the DCFH-DA assay, was significantly higher in treated cells compared to untreated controls. the results of ROS production in three bacterial strains (Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii) when exposed to different concentrations of curcumin. At **16 µg/mL**, ROS production was classified as low for all three bacterial strains, indicating minimal oxidative stress. At **32 µg/mL**, the ROS production increased to a moderate level, suggesting that curcumin begins to induce oxidative stress at this concentration. The highest concentration tested, **64 µg/mL**, resulted in **high ROS production** across all strains, demonstrating a significant increase in oxidative stress. This pattern of dose-dependent ROS production indicates that curcumin's antimicrobial effect may be partly due to the generation of reactive oxygen species, which can damage bacterial cells table 2. These findings support the hypothesis that curcumin induces oxidative stress as a key mechanism underlying its antimicrobial action against multidrug-resistant Gram-negative bacteria.

Table 2

Reactive Oxygen Species (ROS) generation induced by curcumin in MDR Gram-negative pathogens.

Pathogen	Curcumin Concentration (µg/mL)	ROS Production (Fluorescence Intensity)
Pseudomonas aeruginosa	16	Low
	32	Moderate
	64	High
Klebsiella pneumoniae	16	Low
	32	Moderate
	64	High
Acinetobacter baumannii	16	Low
	32	Moderate
	64	High

Cytotoxicity Evaluation

The cytotoxicity of curcumin was assessed on human keratinocyte (HaCaT) cell lines using the MTT assay. Curcumin was tested at concentrations ranging from 1 µg/mL to 128 µg/mL. At 1 µg/mL, 8 µg/mL, 16 µg/mL, and 32 µg/mL, curcumin shows no significant cytotoxicity, with cell viability consistently remaining above 80%. These concentrations have little to no impact on the viability of the cells, indicating that curcumin is well-tolerated at lower doses and does not cause harm to the cells. At 64 µg/mL, cell viability decreases to around 60%, indicating moderate cytotoxicity. This suggests that while curcumin begins to have an impact on cell viability at this concentration, the effect is not severe, and a significant portion of the cells still remain viable. At 128 µg/mL, curcumin shows significant cytotoxicity, with cell viability falling below 50% . This represents a considerable decrease in cell survival, indicating that at higher concentrations, curcumin can become toxic to cells shown in table 3.

Table 3

Cytotoxicity evaluation of curcumin on mammalian cells, showing cell viability percentages at varying concentrations of curcumin (up to 256 µg/mL) as determined by resazurin assay.

Curcumin Concentration (µg/mL)	Cell Viability (%)	Cytotoxicity Effect	Observations
1 µg/mL	>80	No significant cytotoxicity	No notable decrease in cell viability.

8 µg/mL	>80	No significant cytotoxicity	Cell viability remains above 80%.
16 µg/mL	>80	No significant cytotoxicity	No effect on cell viability.
32 µg/mL	>80	No significant cytotoxicity	Cell viability remains above 80%.
64 µg/mL	~60	Moderate cytotoxicity	Cell viability decreases moderately.
128 µg/mL	<50	Significant cytotoxicity	Cell viability below 50%.

DISCUSSION

The results from this study, which evaluated the antimicrobial activity, biofilm inhibition, ROS generation, and cytotoxicity of curcumin, align with and expand upon existing literature on curcumin's potential as a therapeutic agent against multidrug-resistant (MDR) Gram-negative bacteria. Curcumin demonstrated antimicrobial activity against *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii*, with MIC values ranging from 16 µg/mL to 128 µg/mL. The MICs observed in this study are comparable to those reported in other investigations. (Negi, Prakash, Gupta, & Mohapatra, 2014) observed MIC values of 64 µg/mL for *P. aeruginosa* and *A. baumannii*, which is consistent with the findings of this study. Additionally, (Hussain et al., 2022) reported an MIC of 32 µg/mL for *K. pneumoniae*, also aligning with our results. These studies demonstrate that curcumin has a varying degree of efficacy depending on the bacterial strain. The interaction between curcumin and conventional antibiotics was assessed using the checkerboard assay, revealing a strong synergistic effect with ciprofloxacin against *P. aeruginosa* (FICI = 0.25), and an additive effect with ceftazidime against *K. pneumoniae* and *A. baumannii* (FICI = 0.5 and 0.75, respectively). These findings are consistent with previous research by (Betts & Wareham, 2014), who demonstrated that curcumin synergized with antibiotics like ciprofloxacin to improve the antimicrobial effects against *P. aeruginosa*. Similarly, (Sharahi et al., 2020) reported additive effects when curcumin was combined with cephalosporins against Gram-negative pathogens. This reinforces the idea that curcumin may serve as an adjunct to conventional antibiotics, potentially reducing resistance in MDR pathogens. Curcumin demonstrated significant biofilm inhibition at concentrations ranging from 16 µg/mL to 64 µg/mL, with up to a 50% reduction in biofilm biomass for *P. aeruginosa* and *K. pneumoniae* at 32 µg/mL. At higher concentrations (64–128 µg/mL), 60-70% reduction in biofilm biomass was observed. These findings are consistent with (Abdulrahman, Misba, Ahmad, & Khan, 2020), who reported that curcumin could inhibit biofilm formation in *P. aeruginosa* by up to 50% at concentrations of 32 µg/mL. Additionally, (Raorane et al., 2019) demonstrated that curcumin disrupted biofilms of *A. baumannii* and *K. pneumoniae* at similar concentrations, supporting the biofilm-disrupting potential of curcumin seen in our study. The study found dose-dependent ROS production in *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*, with high ROS production at 64 µg/mL. This suggests that curcumin induces oxidative stress, a potential mechanism for its antimicrobial effects. This observation aligns with findings from (Recacha et al., 2019), who noted that curcumin increases ROS production in *E. coli* and other Gram-negative bacteria at concentrations above 50 µg/mL. Similarly, (Song, Wu, Wang, & Han, 2019) reported that curcumin's antimicrobial effects were attributed, in part, to ROS generation, which disrupts bacterial cell integrity. The cytotoxicity of curcumin was assessed using human keratinocyte (HaCaT) cell lines, revealing no significant cytotoxicity at concentrations up to 32 µg/mL, with cell viability remaining above 80%. At 64 µg/mL, cell viability decreased to 60%, and at 128 µg/mL, it fell below 50%, indicating significant cytotoxicity. These results are consistent with (Zhao et al., 2013), who observed that curcumin had a low cytotoxicity profile at concentrations below 50 µg/mL but showed increased cytotoxicity at higher concentrations. Moreover, (Kumar, Aggarwal, Prakash, & Sahoo, 2023) reported similar findings, with moderate cytotoxicity observed at curcumin concentrations of 64 µg/mL.

CONCLUSION

The results from this study confirm curcumin's antimicrobial potential against MDR Gram-negative pathogens, its ability to disrupt biofilms, and its role in inducing oxidative stress through ROS generation. Furthermore, curcumin's cytotoxicity profile indicates that it is safe at lower concentrations but becomes cytotoxic at higher doses. These findings support the ongoing research into curcumin as a potential adjunct to conventional antibiotics, particularly in the treatment of chronic skin infections caused by MDR bacteria.

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