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Antibacterial Efficacy of Curcumin against Multidrug-Resistant Bacteria Isolated from Diabetic Foot Infections: An In Vitro Study

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Abstract

Background

Diabetic foot infection (DFI) represents a major global clinical challenge, frequently complicated by the emergence of multidrug-resistant (MDR) bacterial pathogens. Curcumin, a natural polyphenolic compound derived from *Curcuma longa*, possesses broad-spectrum antimicrobial activity; however, its specific efficacy against clinical MDR pathogens isolated exclusively from DFIs remains insufficiently evaluated. This study aimed to investigate the *in vitro* antibacterial activity of Curcumin against MDR bacterial strains isolated from infected diabetic foot ulcers.

Methods

A total of 54 non-duplicate bacterial isolates were recovered from 30 patients presenting with clinically infected DFIs at a tertiary care center. Species identification was performed using standard biochemical testing and confirmed via the VITEK 2 Compact automated system. Antimicrobial susceptibility testing was conducted using the disk diffusion method according to Clinical and Laboratory Standards Institute (CLSI M100) guidelines. Minimum inhibitory concentrations (MICs) of curcumin (0.5–512 ug/mL) were determined using the broth microdilution technique. *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 served as quality control strains.

Results

The isolates comprised *Staphylococcus aureus* (n = 25, 46.3%), *Klebsiella pneumoniae* (n = 15, 27.8%), *Pseudomonas aeruginosa* (n = 8, 14.8%), *Acinetobacter baumannii* (n = 4, 7.4%), and *Enterobacter cloacae* (n = 2, 3.7%). All 54 isolates exhibited an MDR phenotype. Curcumin demonstrated consistent antibacterial activity against all tested isolates, with MICs ranging from 32 to 128 ug/mL. Gram-positive isolates (*S. aureus*) displayed two-fold higher susceptibility (MIC range: 32–64 ug/mL) compared to Gram-negative species (64–128 ug/mL). Carbapenem-resistant non-fermenting bacilli (*P. aeruginosa* and *A. baumannii*) exhibited MICs of 128 ug/mL.

Conclusions

Curcumin exhibits robust *in vitro* activity against MDR pathogens isolated from DFIs at concentrations achievable via modern topical formulations. These findings warrant further investigation into bio-enhanced topical vehicles and controlled clinical trials to evaluate its potential as an adjunctive antimicrobial strategy in DFI management.

Introduction

Diabetes mellitus affects over 400 million individuals globally, with diabetic foot ulceration (DFU) remaining one of its most severe and costly complications [1, 2]. Approximately 19% to 34% of diabetic patients develop a DFU during their lifetime, leading to significant morbidity, prolonged hospitalizations, and lower-limb amputations [1, 2]. Up to 40% of healed ulcers recur within one year, imposing a heavy burden on healthcare systems worldwide [1].

Infection is a critical factor impairing DFU healing [3]. The microbiological profile of diabetic foot infections (DFIs) is complex and often polymicrobial [3]. Gram-positive cocci, primarily *Staphylococcus aureus*, dominate acute superficial lesions, whereas chronic and deep ulcers frequently harbor Enterobacterales (*Klebsiella pneumoniae*, *Enterobacter* spp.) and non-fermenting Gram-negative bacilli (*Pseudomonas aeruginosa*, *Acinetobacter baumannii*) [3]. Standard clinical management relies heavily on systemically administered antibiotics; however, therapeutic efficacy is progressively compromised by the rising prevalence of multidrug-resistant (MDR) strains—defined as resistance to at least one agent in three or more antimicrobial categories [4]. High carriage rates of methicillin-resistant *S. aureus* (MRSA) and extended-spectrum beta-lactamase (ESBL)- or carbapenemase-producing Gram-negative bacteria in DFIs are directly associated with treatment failure and elevated mortality rates [5, 6].

To combat the escalating threat of antimicrobial resistance (AMR), interest has intensified toward plant-derived bioactive compounds with novel mechanisms of action [7, 8]. Curcumin (diferuloylmethane), a hydrophobic polyphenol extracted from the rhizome of *Curcuma longa*, exhibits diverse pharmacological properties, including antioxidant, anti-inflammatory, pro-wound healing, and broad-spectrum antimicrobial activities [7, 8]. The antibacterial mode of action of curcumin is multifactorial: it disrupts bacterial cell membrane integrity, inhibits FtsZ protofilament assembly, attenuates quorum sensing and biofilm formation, induces intracellular reactive oxygen species (ROS) accumulation, and downregulates efflux pump activity [7, 10, 11]. Because it targets multiple essential cellular processes simultaneously, the probability of rapid bacterial resistance development is substantially lower than that observed with single-target synthetic antibiotics [12, 13].

Although previous studies have documented the antimicrobial potential of curcumin, much of the existing data relies on reference ATCC strains or heterogeneous clinical isolates non-specific to DFIs [5, 6, 16, 17]. Furthermore, methodological variations in solvent vehicle selection and inoculum preparation have hindered inter-study comparability. Therefore, this study aimed to systematically evaluate the *in vitro* antibacterial efficacy of standardized curcumin against a panel of clinically derived MDR bacteria isolated from patients with DFIs, following standard CLSI broth microdilution guidelines.

Materials and Methods

Study Design and Bacterial Strain Source

This prospective *in vitro* study evaluated bacterial strains isolated from adult patients (age ≥ 18 years) diagnosed with clinically infected DFIs (defined by purulent drainage, local erythema, warmth, or induration) attending a tertiary care facility between January and June 2020. Ethical approval was granted by the Institutional Review Board, and informed consent was obtained prior to specimen collection. Patients with superficial non-infected ulcers or insufficient exudate volume were excluded.

Isolation and Identification

Wound exudate samples were obtained following gentle saline irrigation and surgical debridement (when necessary) using sterile cotton swabs inserted into the deepest portion of the wound bed. Swabs were transported in Amies transport medium and processed within 1 h. Samples were inoculated onto 5% sheep blood agar and MacConkey agar (HiMedia, Mumbai, India) and incubated aerobically at 37°C for 24–48 h. Distinct morphological colonies (up to 3 per patient) were subcultured to purity. Phenotypic identification was performed

via standard biochemical methods (Gram stain, catalase, oxidase, coagulase, indole, citrate, urease, and TSI assays) and confirmed using VITEK 2 Compact automated identification cards (bioMérieux, Marcy-l'Étoile, France) according to manufacturer instructions.

Antimicrobial Susceptibility Testing and MDR Phenotyping

Antimicrobial susceptibility testing was carried out using the Kirby–Bauer disk diffusion technique on Mueller–Hinton agar (MHA; HiMedia) in accordance with CLSI M100 guidelines [18]. Bacterial suspensions adjusted to 0.5 McFarland standard (≈ 1.5×10^8 CFU/mL) were uniformly inoculated onto MHA plates. A panel of 10 commercial antibiotic disks representing beta-lactams, fluoroquinolones, aminoglycosides, and carbapenems was applied. Plates were incubated at 16–18 h at 35 ± 2°C. Inhibition zone diameters were measured and classified as susceptible, intermediate, or resistant per CLSI interpretive criteria [18]. Strains exhibiting resistance to 3 or more agent in three or more antimicrobial classes were classified as MDR [4].

Determination of Minimum Inhibitory Concentration (MIC) of Curcumin

Purified curcumin (purity ≥ 94%, Sigma-Aldrich, St. Louis, MO, USA) was dissolved in dimethyl sulfoxide (DMSO) to prepare stock solutions, which were filter-sterilized and stored in light-protected containers. Serial two-fold broth microdilution assays were performed in Mueller–Hinton broth (MHB) across a concentration range of 0.5–512 µg/mL in 96-well microtiter plates. Final DMSO concentrations in all test wells were maintained below 2.5% (v/v) —a concentration previously verified to exert no inhibitory effect on bacterial viability [10].

Inocula were added to yield a final well density of approximately 5 × 105 cfu/mL. Microtiter plates were incubated at 37°C for 24 h. MIC was defined as the lowest concentration of curcumin that completely inhibited visible bacterial growth. Solvent controls (MH broth with 2.5% DMSO) and sterile controls were included in each run. Assays were performed in duplicate; discordant results were resolved by a third independent replicate. *Staphylococcus aureus* ATCC 29213 and *Escherichia coli* ATCC 25922 served as reference strain controls [18].

Statistical Analysis

Data were summarized using descriptive statistics. Categorical variables (species prevalence, resistance profiles) were reported as counts and percentages (%). MIC values were presented as ranges and modal concentrations. Differences in susceptibility between Gram-positive and Gram-negative groups were evaluated based on standard doubling-dilution fold differences.

Results

Isolate Distribution and Microbial Profiles

A total of 54 non-duplicate bacterial strains were recovered from 30 DFI patients (mean yield: 1.8 isolates per sample). Gram-negative bacilli represented 53.7% (n = 29) of the isolates, while Gram-positive cocci accounted for 46.3% (n = 25). *Staphylococcus aureus* was the single most prevalent pathogen (n = 25, 46.3%), followed by *Klebsiella pneumoniae* (n = 15, 27.8%), *Pseudomonas aeruginosa* (n = 8, 14.8%), *Acinetobacter baumannii* (n = 4, 7.4%), and *Enterobacter cloacae* (n = 2, 3.7%) (**Table 1**).

Table 1. Distribution and multidrug resistance status of bacterial isolates from diabetic foot infections (N = 54).

Bacterial Species	Gram Reaction	Total Isolates, n (%)	MDR Isolates, n (%)
Staphylococcus aureus	Positive	25 (46.3%)	25 (100%)
Klebsiella pneumoniae	Negative	15 (27.8%)	15 (100%)
Pseudomonas aeruginosa	Negative	8 (14.8%)	8 (100%)
Acinetobacter baumannii	Negative	4 (7.4%)	4 (100%)
Enterobacter cloacae	Negative	2 (3.7%)	2 (100%)
Total	—	**54 (100.0%)**	**54 (100%)**

Abbreviation: MDR, multidrug-resistant (resistance to three or more antimicrobial classes).

Antimicrobial Resistance Profiles

All 54 isolates (100%) met the criteria for multidrug resistance (**Table 2**). Complete resistance to tested beta-lactams was observed across all species. *S. aureus* and *K. pneumoniae* isolates exhibited concurrent resistance to fluoroquinolones and aminoglycosides. *P. aeruginosa* and *A. baumannii* isolates displayed resistance to carbapenems.

Table 2. Antimicrobial class resistance patterns of clinical DFI isolates.

Bacterial Species	β-Lactams	Fluoroquinolones	Aminoglycosides	Carbapenems	Resistant Classes (n)	MDR Status
Staphylococcus aureus	R	R	R	NT	3	Yes
Klebsiella pneumoniae	R	R	R	NT	3	Yes
Pseudomonas aeruginosa	R	R	NT	R	3	Yes
Acinetobacter baumannii	R	NT	R	R	3	Yes
Enterobacter cloacae	R	R	R	NT	3	Yes

Legend: R, resistant to at least one tested agent in the class; NT, not tested or not reported; MDR, multidrug-resistant.

Minimum Inhibitory Concentrations (MICs) of Curcumin

Curcumin inhibited the growth of all 54 MDR isolates, with MIC values ranging between 32 and 128 ug/mL (**Table 3**). Gram-positive *S. aureus* isolates were the most sensitive, displaying MICs of 32–64 ug/mL. Enterobacterales (*K. pneumoniae* and *E. cloacae*) exhibited intermediate susceptibility (64–128 ug/mL). Non-fermenting Gram-negative bacilli (*P. aeruginosa* and *A. baumannii*) consistently demonstrated an MIC of 128 ug/mL. Overall, Gram-

positive bacteria displayed a 2-fold higher susceptibility (one-to-two doubling dilutions lower) compared to Gram-negative pathogens. Vehicle control wells containing 2.5% DMSO showed no growth inhibition.

Table 3. Minimum inhibitory concentrations (MICs) of curcumin against MDR DFI isolates.

Species	No. of Isolates	MIC Range (µg/mL)	Modal MIC (µg/mL)	Relative Susceptibility	Fold-Difference vs. S. aureus
Staphylococcus aureus	25	32–64	32	High	Baseline
Klebsiella pneumoniae	15	64–128	64	Intermediate	1–2 fold higher
Enterobacter cloacae	2	64–128	64	Intermediate	1–2 fold higher
Pseudomonas aeruginosa	8	128	128	Moderate	2 fold higher
Acinetobacter baumannii	4	128	128	Moderate	2 fold higher

Discussion

The rapid dissemination of multidrug resistance among DFI pathogens presents a severe clinical therapeutic bottleneck [4,5]. The present study demonstrates that pure curcumin possesses robust *in vitro* antibacterial activity against a panel of clinically isolated MDR pathogens recovered from DFIs, with MIC values ranging from 32 to 128 ug/mL. Importantly, all isolates were susceptible within a concentration range achievable through modern topical drug delivery systems [9,23].

The microbial profile observed in this cohort mirrors global epidemiological patterns for DFIs, characterized by a high prevalence of *S. aureus*, *K. pneumoniae*, and non-fermenting Gram-negative bacilli [3,6]. However, the universal MDR phenotype recorded in this study underscores the intense selection pressure operating within chronic, antibiotic-exposed wound beds [4,5]. The presence of carbapenem resistance among *P. aeruginosa* and *A. baumannii* isolates is particularly concerning, as carbapenems often serve as last-resort therapies for severe polymicrobial soft-tissue infections [4].

Our findings confirm a consistent two-fold difference in susceptibility between Gram-positive and Gram-negative isolates [5,10]. Gram-positive *S. aureus* exhibited the lowest MICs (32–64 ug/mL, whereas Gram-negative species required concentrations of 64–128ug/mL. This differential susceptibility is attributable to fundamental structural variations in cell wall architecture [10,15]. Gram-negative bacteria possess an outer lipopolysaccharide (LPS) membrane that acts as a hydrophilic permeability barrier, restricting the passive influx of hydrophobic molecules such as curcumin. Conversely, the single peptidoglycan layer of Gram-positive organisms allows readier access of curcumin to the cytoplasmic membrane [7,10].

Curcumin's antibacterial activity relies on membrane destabilization, inhibition of cell division proteins (FtsZ), generation of lethal reactive oxygen species, attenuation of quorum sensing, and suppression of active efflux pumps [7,10,11,12]. Because these mechanisms operate non-specifically across multiple structural targets, curcumin poses a low risk for selecting primary single-gene resistance mechanisms [12,13].

Although native curcumin exhibits limited systemic bioavailability following oral administration, topical application circumvents metabolic clearance, enabling direct delivery of elevated concentrations to infected tissue beds [9,23]. Free curcumin suffers from poor aqueous solubility, rapid photodegradation, and brief exudative residence time. Recent bio-engineering innovations—such as chitosan nanoparticles, electrospun nanofibrous meshes, lipid nanocarriers, and hydrogel dressings—effectively overcome these physicochemical constraints, ensuring sustained release and enhanced stability at the wound site (**Table 4**) [17,22-25].

Table 4. Summary of recent literature on Curcumin-based interventions in DFI and wound management.

Study	Formulation / Model	Primary Findings
Nazari et al. (2025) [17]	Free natural products review	Highlighted curcumin as a top candidate for DFI with antibacterial, antibiofilm, and pro-healing capacity.
Gómez-de la Cruz et al. (2026) [23]	Chitosan-nanoencapsulated curcumin	Enhanced aqueous solubility and superior antibacterial/anti-inflammatory activity in DFU models.
Baligod et al. (2026) [24]	Hydrogel / Nanofiber hybrid dressings	Synergistic combination of curcumin with delivery systems optimizes local clinical efficacy.
Sanpinit et al. (2024) [25]	*Curcuma longa* polyherbal formulation (RCT)	Achieved 76% wound healing at 12 weeks vs. 16% in standard care control ($p < 0.001$).
Present Study (2026)	*In vitro* microdilution (54 MDR clinical isolates)	Demonstrated universal MIC inhibition at 32–128 ug/mL.

Limitations

Several limitations of this study should be acknowledged. First, the sample size was small (N = 54), precluding formal MIC estimations or species-specific statistical subgroup analyses. Second, molecular characterization of resistance genes (e.g., bla *mecA*) and specific efflux pump assays were not performed. Third, fractional inhibitory concentration index (FICI) checkerboard assays and time-kill kinetics were not conducted to test for synergy with conventional antibiotics. Finally, *in vitro* broth conditions do not fully replicate the complex microenvironment of chronic polymicrobial biofilm-bearing diabetic wounds.

Conclusion

Curcumin exhibits significant *in vitro* antibacterial activity against multidrug-resistant clinical isolates from diabetic foot infections, demonstrating complete growth inhibition across all tested strains at concentrations of 32–128 ug/mL. Given that these concentrations are readily deliverable via advanced topical nano-formulations, curcumin represents a promising adjunctive candidate to combat antibiotic-resistant wound infections. Future research should emphasize synergy testing with standard-of-care antibiotics, biofilm eradication assays, and phase II clinical evaluation of nano-engineered topical formulations.

Declarations

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee.

Informed Consent Statement:

Informed consent was obtained from all individual participants included in the study.

Conflicts of Interest:

The authors declare no conflicts of interest.

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Author Contribution

A: RESEARCH IDEA , INTRODUCTION B: MATERIALS AND METHODS C: RESULTS AND STATISTICAL ANALYSIS D: DISCUSSION, REFERENCES AND PUBLISHING PROCESS

Data Availability Statement:

Data supporting the reported results are available from the corresponding author upon reasonable request.

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