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POLYPHENOL–GENTAMICIN SYNERGY AGAINST MULTIDRUG-RESISTANT GRAM-NEGATIVE BACTERIA

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Abstract

Antimicrobial resistance in Gram-negative ESKAPE pathogens demands adjuvant strategies that restore first-line antibiotics. We screened ten natural polyphenols against 32 MDR/XDR clinical isolates of Klebsiella pneumoniae, Acinetobacter baumannii and Pseudomonas aeruginosa, combining broth microdilution, checkerboard FICI, time-kill and crystal-violet biofilm assays. Gallic acid and quercetin displayed the strongest intrinsic activity, while gallic acid- and curcumin-gentamicin pairs produced consistent synergy, reducing gentamicin MICs 4- to 16-fold and resensitizing high-level resistant strains. Synergistic combinations achieved rapid bactericidal killing with durable suppression of regrowth over 24 h and curtailed biofilm formation by up to 82% at sub-inhibitory concentrations. These findings position selected polyphenols as rational aminoglycoside adjuvants and provide a translational basis for polyphenol–antibiotic combinations against critical Gram-negative resistance.

Key words: *antimicrobial resistance; biofilm; gentamicin; polyphenols; synergy.*

INTRODUCTION

The global dissemination of antimicrobial resistance (AMR) among Gram-negative bacteria constitutes a formidable challenge to modern medicine (Javadimarand et al., 2026; Murray et al., 2022). The ESKAPE pathogens, notably *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, are frequently implicated in severe nosocomial infections (Gebeyehu et al., 2026; Sakalauskienė et al., 2025), including ventilator-associated pneumonia, bloodstream infections, and complicated urinary tract infections (De Oliveira et al., 2020). These organisms possess a remarkable repertoire of intrinsic and acquired resistance mechanisms (Pandey et al., 2025), such as the production of extended-spectrum beta-lactamases (Akter et al., 2026) and carbapenemases, overexpression of multidrug efflux pumps (Miftode et al., 2026), and the modification of outer membrane porins (Miller & Arias, 2024). Furthermore, their ability to form robust biofilms on biotic and abiotic surfaces significantly enhances their tolerance to antimicrobial agents and host immune responses (Sharma et al., 2026; Zdarska et al., 2026), leading to chronic and recurrent infections (Sarkar et al., 2024).

Aminoglycosides, such as gentamicin, have historically been a cornerstone in the treatment of severe Gram-negative infections (Erdem & Yilmaz-Tehli, 2026; Franco-Moreno et al., 2026) due to their rapid bactericidal concentration-dependent activity (Qureshi et al., 2025; Krause et al., 2016). However, their clinical utility is increasingly compromised by the widespread emergence of aminoglycoside-modifying enzymes (Alikani et al., 2025) and the up-regulation of efflux systems (Garneau-Tsodikova et al., 2016). Additionally, the narrow therapeutic index of aminoglycosides, associated with nephrotoxicity and ototoxicity, limits the feasibility of simply increasing the administered dose to overcome resistance

(Zadrożniak et al., 2025; Wargo & Edwards, 2014).

In this context, the concept of adjuvant therapy or combination therapy using non-antibiotic compounds to restore the efficacy of existing antibiotics has gained significant traction (Wright, 2016). Natural polyphenols, a diverse class of plant secondary metabolites, have emerged as promising candidates (Shahnawaz et al., 2026). These compounds exhibit a wide range of biological activities, including intrinsic antimicrobial properties (Talha & Roque-Borda, 2026) and the ability to modulate bacterial resistance mechanisms (Manso et al., 2021). Polyphenols can perturb the bacterial outer membrane (Hamza et al., 2026), inhibit efflux pumps (Nappa et al., 2026), interfere with quorum sensing systems (Lima et al., 2025) and generate reactive oxygen species (Rao & Zheng, 2025), thereby sensitizing bacteria to conventional antibiotics (De Rossi et al., 2025).

This study aims to systematically evaluate the intrinsic antimicrobial activity of a diverse library of ten natural polyphenols and to rigorously quantify their synergistic interactions with gentamicin against a well-characterized collection of clinical MDR and XDR strains of *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa.*

MATERIALS AND METHODS

The research was conducted between May 2024 and February 2026 in the Microbiology Laboratory of the Faculty of Biology, University of Bucharest.

A total of 32 clinical strains (12 *K. pneumoniae*, 10 *A. baumannii*, 10 *P. aeruginosa*) were isolated from patients with severe nosocomial infections. The strains were characterized as MDR or XDR based on standard clinical susceptibility testing. Bacteria were routinely cultured in Tryptic Soy Broth or on Mueller-Hinton Agar at 37°C.

Gentamicin sulfate and ten natural polyphenols (gallic acid, curcumin, quercetin, resveratrol, epicatechin, kaempferol, caffeic acid, ferulic acid, vanillic acid, and p-coumaric acid) of analytical grade (≥95% purity) were utilized. Stock solutions were prepared in appropriate solvents and diluted in culture media prior to use, ensuring that the final solvent concentration did not exceed 1% (v/v) to avoid solvent-induced toxicity.

The intrinsic antimicrobial activity of the polyphenols and gentamicin was evaluated by determining the MIC using the broth microdilution method in 96-well microtiter plates, according to the Clinical and Laboratory Standards Institute guidelines. The MIC was defined as the lowest concentration of the compound that completely inhibited visible bacterial growth after 18-24 h of incubation at 37°C.

The synergistic interactions between the most active polyphenols (gallic acid, quercetin, curcumin, and resveratrol) and gentamicin were evaluated using the checkerboard microdilution method. Serial two-fold dilutions of the polyphenol and gentamicin were combined in a 96-well plate to create a matrix of varying concentration combinations. The fractional inhibitory concentration index was calculated as FICI = (MIC of drug A in combination/MIC of drug A alone) + (MIC of drug B in combination / MIC of drug B alone). Synergy was defined as FICI $\leq$ 0.5, additivity as 0.5 < FICI $\leq$ 1.0, indifference as 1.0 < FICI $\leq$ 4.0, and antagonism as FICI > 4.0.

Time-kill assays were performed to evaluate the dynamic bactericidal activity of the synergistic combinations over 24 h. Bacterial cultures (initial inoculum approximately 10^6 CFU/mL) in cation-adjusted Mueller-Hinton broth were exposed to gentamicin alone, polyphenol alone, and their combination at specific sub-inhibitory concentrations (e.g., MIC/2). Aliquots were removed at predetermined time points (0, 4, 8, 12, 24 h), serially diluted, and plated on Mueller-Hinton Agar for colony counting. A bactericidal effect was defined as a ≥3 log10 CFU/mL reduction compared to the initial inoculum.

The effect of the treatments on biofilm formation was evaluated using the crystal violet assay. Briefly, bacterial suspensions were incubated in 96-well plates in the presence of sub-inhibitory concentrations of the agents alone or in combination. After 24 h, planktonic cells were removed, and adherent biofilm biomass was stained with 0.1% crystal violet, solubilized in 33% acetic acid, and quantified by measuring the optical density at 595 nm.

All experiments were performed in triplicate. Data are presented as mean ± standard deviation. Statistical significance was determined using one-way analysis of variance followed by Tukey's post hoc test, with $p < 0.05$ considered statistically significant. The overall experimental workflow and analytical structure of the study are summarized in Figure 1.

RESULTS AND DISCUSSIONS

The screening of the ten polyphenols revealed structure-dependent variations in antimicrobial efficacy. Gallic acid demonstrated the most potent and consistent activity across all three species, with median MIC values of 128 µg/mL for *K. pneumoniae,* 64 µg/mL for *A. baumannii,* and 256 µg/mL for *P. aeruginosa.* Quercetin also exhibited notable activity, with median MIC values ranging from 128 to 512 µg/mL across the examined species. *A. baumannii* was generally the most susceptible species to the tested polyphenols, whereas *P. aeruginosa* exhibited the highest intrinsic resistance. A consolidated cross-species synopsis of the principal quantitative findings is provided in Table 1, while the most relevant numerical trends are visualized in Figure 1.

Table 1. Intrinsic antimicrobial activity and synergy profile of selected polyphenols combined with gentamicin against MDR/XDR Gram-negative clinical isolates

Polyphenol or Combination	Biological Context	Reported Quantitative Finding	Interpretive Note
Gallic acid	*K. pneumoniae*	Median MIC = 128 µg/mL	Most active polyphenol against this species among the tested library
Gallic acid	*A. baumannii*	Median MIC = 64 µg/mL	Lowest reported gallic acid MIC among the three species; highest susceptibility
Gallic acid	*P. aeruginosa*	Median MIC = 256 µg/mL	Highest intrinsic resistance to gallic acid among the three species
Quercetin	Species panel	Median MICs = 128–512 µg/mL	Notable intrinsic activity, but less consistently potent than gallic acid
Gallic acid + gentamicin	Tested strains	Synergy in 87.5% of strains; 4- to 16-fold gentamicin MIC reduction	Most robust combinational effect reported in the study
Curcumin + gentamicin	Tested strains	Synergy reported in the majority of tested strains	Promising adjuvant effect supporting aminoglycoside rescue
Quercetin or epicatechin + gentamicin	Tested strains	Significant synergistic or additive effects	Adjunctive activity was present, but less extensively quantified than for gallic acid
Gallic acid/gentamicin combination	XDR K. pneumoniae KP-04	>3 log10 CFU/mL reduction within 6 h; eradication by 12 h; no regrowth to 24 h	Rapid and sustained bactericidal activity in the representative time-kill experiment
Sub-inhibitory combination	*K. pneumoniae* biofilm	82% biofilm inhibition versus 25-35% for single agents	Marked enhancement of antibiofilm performance under combination exposure

The checkerboard assay revealed synergistic interactions between specific polyphenols and gentamicin. Gallic acid exhibited the strongest synergy, with FICI values ≤ 0.5 observed in 87.5% of the tested strains. The combination of gallic acid and gentamicin resulted in a 4- to 16-fold reduction in the MIC of the antibiotic. Quercetin and epicatechin also demonstrated significant synergistic or additive effects. The synergistic effect was most pronounced in strains exhibiting high-level baseline resistance to gentamicin (MIC > 16 µg/mL), suggesting

that the polyphenols effectively neutralize acquired resistance mechanisms. The frequency and quantitative scale of the most robust gallic acid–gentamicin interaction are summarized in Figure 2.

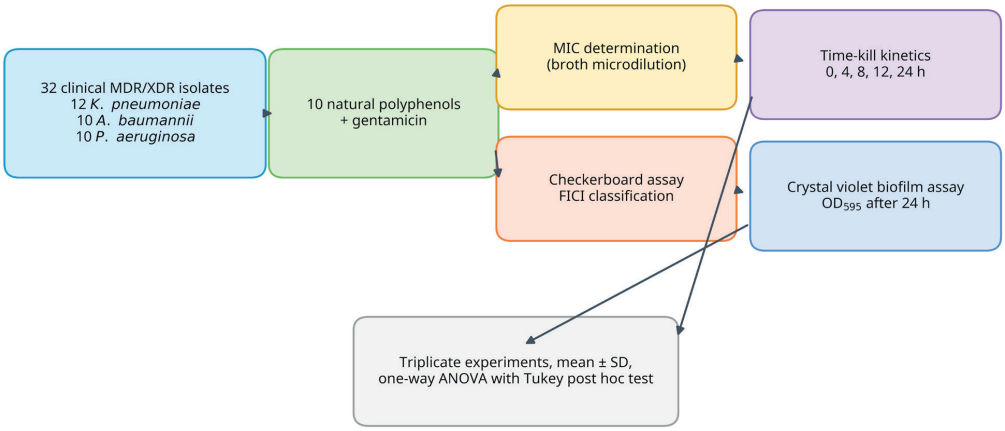


Figure 1. Experimental workflow and analytical structure of the study. The scheme summarizes isolate selection, the tested compound library, MIC determination, checkerboard-based FICI analysis, time-kill kinetics, antibiofilm testing, and the final statistical workflow

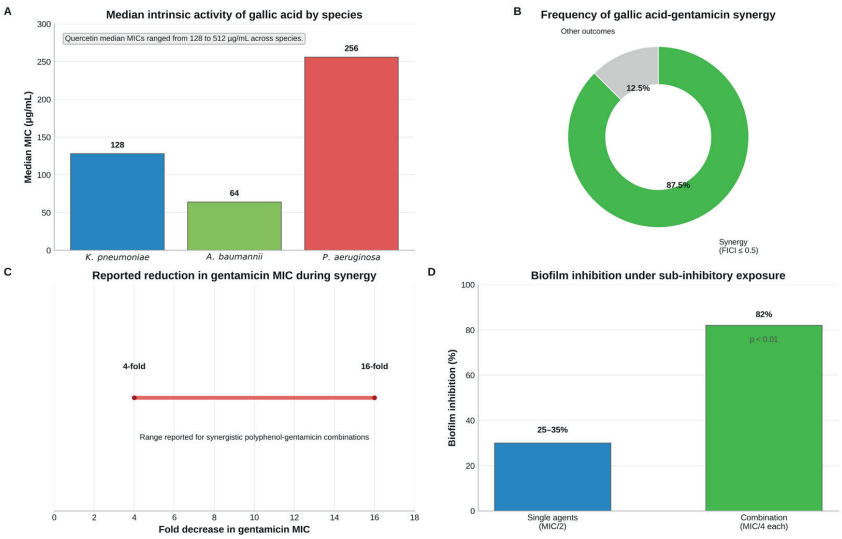


Figure 2. Quantitative summary of the leading polyphenol-gentamicin findings reported in the manuscript. Panel A shows species-resolved gallic acid MIC values. Panel B summarizes the frequency of gallic acid–gentamicin synergy. Panel C shows the reported range of gentamicin MIC reduction in synergistic combinations. Panel D compares single-agent and combination antibiofilm performance

Time-kill assays confirmed the rapid and sustained bactericidal activity of the synergistic combinations. Against the XDR *K. pneumoniae* strain KP-04, gentamicin alone at MIC/2 exhibited only a transient bacteriostatic effect followed by rapid regrowth. In contrast, the combination of gentamicin and gallic acid, both used at MIC/2, achieved a bactericidal effect exceeding a 3 log10 reduction within 6 h and completely eradicated the bacterial population below the limit of detection by 12 h, with no recrudescence observed up to 24 h. A time-resolved schematic summary of this representative experiment is presented in Figure 3.

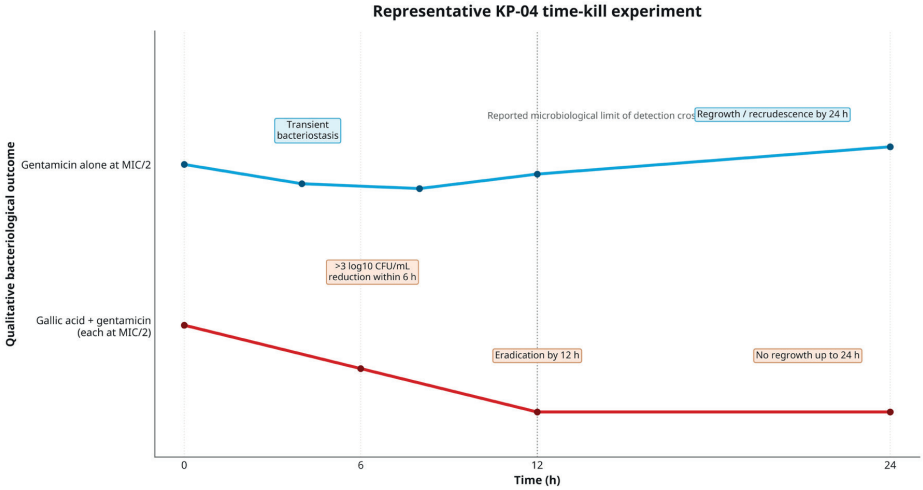


Figure 3. Time-resolved outcome of the representative KP-04 time-kill experiment. Gentamicin alone at MIC/2 produced only transient bacteriostasis followed by regrowth, whereas the gallic acid–gentamicin combination achieved a bactericidal effect within 6 h, eradication by 12 h, and no regrowth up to 24 h. This figure is a data-faithful schematic reconstruction of the reported outcome and does not infer unreported intermediate colony counts

The synergistic combinations also demonstrated significant anti-biofilm properties. While individual treatments with gallic acid or gentamicin at MIC/2 inhibited biofilm formation by 25-35%, their combination at lower concentrations (MIC/4 each) resulted in an 82% inhibition of biofilm formation in *K. pneumoniae* ($p < 0.01$). This finding suggests that the polyphenols not only facilitate antibiotic entry into planktonic cells but also interfere with the early stages of biofilm development, possibly through quorum-quenching mechanism. The numerical contrast between single-agent and combination exposure is also captured in Figure 1.

The findings of this study provide evidence for the utility of natural polyphenols as adjuvants capable of restoring the efficacy of aminoglycoside antibiotics against MDR Gram-negative pathogens. The synergism observed, particularly with gallic acid and quercetin, highlights the potential of these compounds to overcome the resistance barriers of critical ESKAPE-group organisms. A mechanistic interpretation consistent with the observed microbiological outcomes and the cited literature is summarized in Figure 4.

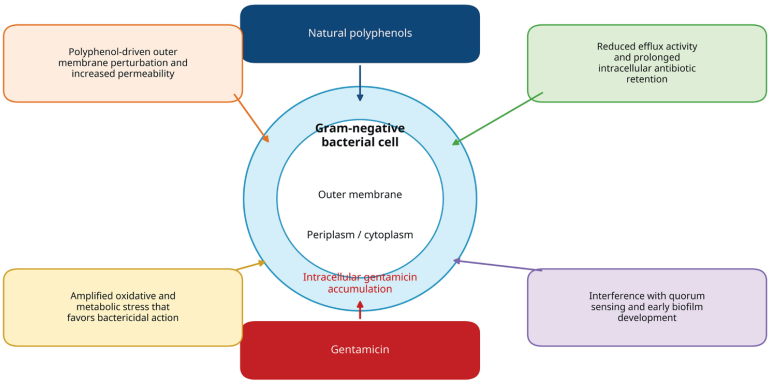


Figure 4. Proposed mechanisms underlying the potentiation of gentamicin by natural polyphenols in Gram-negative pathogens. The model integrates membrane permeabilization, reduced efflux-mediated extrusion, amplification of oxidative stress, and interference with quorum sensing and early biofilm development, in line with the study findings and the cited literature (Duda-Madej et al., 2025; Liang et al, 2026)

The mechanism underlying this synergism is likely multifactorial. Polyphenols, particularly those containing catechol or gallol moieties (Bolaños-Cardet, 2026) can interact with the bacterial outer membrane, destabilizing the lipopolysaccharide layer (Wang et al., 2025) and increasing permeability (Xie et al., 2017). This perturbation can facilitate gentamicin influx by partially bypassing the restricted porin barrier (Hashim et al., 2025). Furthermore, polyphenols have been shown to act as competitive inhibitors of resistance-nodulation-division-type efflux pumps, thereby preventing active antibiotic extrusion and maintaining lethal intracellular concentrations (Ramata-Stunda et al., 2022). In parallel, their capacity to enhance oxidative stress and interfere with quorum sensing may reinforce both bactericidal and antibiofilm outcomes (Ormeanu et al., 2025).

The ability of the synergistic combinations to rapidly eradicate bacterial populations (Fu et al., 2025) and prevent the selection of resistant mutants (Gan et al., 2025), as demonstrated by the time-kill assay, is of direct translational interest (Nath & Rodríguez-Rojas, 2026). Moreover, the anti-biofilm activity suggests that these combinations could be effective in chronic or device-associated infections where conventional monotherapy frequently fails. Collectively, the integrated visual synthesis developed for the present manuscript strengthens the interpretation that polyphenol-assisted aminoglycoside rescue merits further preclinical and mechanistic investigation.

CONCLUSIONS

This study demonstrates that natural polyphenols, specifically gallic acid and quercetin, exhibit synergistic interactions with gentamicin against clinical MDR and XDR strains of *K. pneumoniae*, *A. baumannii*, and *P. aeruginosa*. The combination therapy effectively reduces the required antibiotic dose, restores susceptibility in highly resistant isolates, and exhibits rapid bactericidal and anti-biofilm activity.

These findings support the development of polyphenol-antibiotic combination therapies as a viable strategy to combat the growing threat of antimicrobial resistance.

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