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Assessment of the efficacy of diosmin against methicillin-resistant *Staphylococcus aureus* and the underlying mechanism of action

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ABSTRACT

Objective: To investigate the antibacterial and antibiofilm activities of diosmin, a plant-derived flavonoid glycoside, against clinical isolates of methicillin-resistant *Staphylococcus aureus* (MRSA), in response to the growing challenge of multidrug-resistant bacterial infections.

Methods: The antibacterial activity of diosmin was assessed against five clinical MRSA isolates using broth microdilution method to determine minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC). Antibiofilm activity was evaluated using crystal violet biofilm assay. Additionally, cell viability within biofilms was measured using a triphenyl tetrazolium chloride (TTC) assay.

Results: Diosmin demonstrated a consistent MIC of 1.0 mg/mL and MBC of 2.0 mg/mL across all tested MRSA isolates, indicating primarily bacteriostatic activity at lower concentrations. Biofilm formation was significantly inhibited in a dose-dependent manner, with reductions ranging from 52% to 79% at 1.5 mg/mL. The minimum biofilm inhibitory concentration ($MBIC_{50}$) values ranged from 0.0048 mg/mL to 0.0350 mg/mL. TTC assay results showed that diosmin significantly reduced viable biofilm-embedded cells at concentrations equal to or above the MIC, while sub-MIC concentrations exhibited minimal cytotoxic effects, suggesting non-lethal antibiofilm mechanisms.

Conclusion: Diosmin exhibits promising antibacterial and antibiofilm activities against MRSA, with effective inhibition of biofilm formation and reduction of viable cells. These findings support its potential as a natural alternative or adjunct therapeutic agent for managing MRSA infections.

Keywords: MRSA, diosmin, antibacterial activity, antibiofilm activity, multidrug resistance

INTRODUCTION

Multidrug-resistant bacteria that cause infections are becoming more common, and this creates an imminent risk to global health [1, 2]. There has been a high death rate, disability rate, and sickness rate due to a shortage of recently developed antimicrobial medications, especially in poor nations [3]. It was reported that each year more than 2.8 million antibiotic-resistant illnesses caused 35,000 deaths in the USA [4]. Despite the fact that antibiotics are the most effective treatment for bacterial diseases, bacteria are become resistant to these medications [5, 6]. According to estimates, resistant *Staphylococcus aureus* (*S. aureus*) infections cause about one million fatalities worldwide [7]. *S. aureus* is an opportunistic pathogen that causes high rates of illness and death. It plays a significant role in the development of both minor and serious diseases, such as toxic shock syndrome, infective endocarditis, osteomyelitis, skin and respiratory infections, and toxic shock syndrome [8, 9]. *S. aureus* is one of the clinically major worldwide risks associated with multidrug resistance, according to the World Health Organization's most recent worldwide priority pathogens list of antibiotic-resistant bacteria [10].

Methicillin-resistant, or methicillin-resistant *Staphylococcus aureus* (MRSA), is considered one of the worst antibiotic-resistant bacteria in the USA, which costs the health-care system $3-4 billion annually [11]. Thus, research is still concentrated on MRSA infection control and prevention [12]. Antimicrobial compounds derived from plants offered an effective remedy, despite the fact that their antibacterial efficacy is less than that of conventional antibiotics. As a consequence, herbal components can be used with antibiotics to increase their efficacy against bacterial illnesses [13].

Flavonoids known for its high bioactive components, which poses potent biological actions [14]. These compounds can be found in large amounts in a variety of foods, including fruits, vegetables, whole grains, legumes, beans, herbs, seeds, nuts, tea, and dark chocolate [15, 16]. Their therapeutic value and biological activities are attributed to their presence of bioactive phytochemical constituents. Diosmin compound is also known as diosmetin 7-O-rutinoside is classified as an unsaturated flavonoid glycoside has been previously isolated from citrus fruits [17]. It is a physiologically active polyphenol

Table 1. List of bacterial strains used in antibacterial assessment

Number of clinical isolates	Accession number
MRSA isolate 2	OQ568767
MRSA isolate 4	OQ568769
MRSA isolate 6	OQ568771
MRSA isolate 7	OQ568772
MRSA isolate 9	OQ568774

Note. MRSA: Methicillin-resistant *Staphylococcus aureus*

with anti-inflammatory, antioxidant, hypoglycemic, and mutagenic qualities [18].

Prior studies demonstrated a nephroprotective role for diosmin against alloxan-induced nephropathy in rat models, and its efficiency against alcoholic liver injury [19]. Furthermore, diosmin effectively enhanced cardiac functions and had antihyperlipidemic effects against isopropanol-induced myocardial damage in rats [20]. A search of the literature turned up no credible studies on the defenses of diosmin against MRSA. Consequently, the purpose of this study is to investigate the antibacterial effects of efficacy of diosmin against MRSA and examination of its safety and the underlying mechanism of action.

MATERIALS AND METHODS

Bacterial Culture and Preparation

Clinical isolates of MRSA (MRSA 2, MRSA 4, MRSA 6, MRSA 7, and MRSA 9) were obtained and stored at -80 °C in 20% glycerol. These isolates were previously identified and characterized in previous studies [21, 22]. Prior to experiments, each strain was streaked onto nutrient agar plates and incubated at 37 °C for 18-24 hours. Single colonies were then selected and inoculated into Mueller-Hinton Broth, followed by incubation at 37 °C with shaking at 150 rpm until reaching the logarithmic growth phase (OD600 ≈ 0.5).

Bacterial suspensions were subsequently adjusted to a final concentration of 5×10^5 CFU/mL for minimum inhibitory concentration (MIC), minimum bactericidal concentration (MBC), and biofilm assays. A stock solution of diosmin was prepared by dissolving 10 mg in 1 mL of dimethyl sulfoxide (DMSO). The untreated control culture was prepared similarly. Each test was performed in triplicate. Diosmin was purchased from Biosynth Carbosynth, UK, five strains of MRSA were used in this study to detect antimicrobial and antibiofilm activity of diosmin. Diosmin was purchased from Biosynth Carbosynth, UK. Rregarding the microorganisms, five strains of MRSA were used in this study to detect antimicrobial and antibiofilm activity of diosmin (**Table 1**).

Determination of Minimal Inhibitory Concentration and Minimal Bactericidal Concentration of Diosmin

The broth dilution technique was employed to ascertain the MIC and MBC values of diosmin against MRSA strains, according to early study with some modifications [23]. In 96-well microplates, 100 µL of each diosmin dilution ranging from 5 mg/mL to 0.01 mg/mL was mixed with 90 µL of Mueller Hinton broth and 10 µL of bacterial inoculums. The bacterial inoculum was prepared at 5×10^6 CFU/mL, resulting in a final inoculum concentration of 5×10^5 CFU/mL in each well, in accordance with NCCLS standard methods, with some modifications.

The MIC is defined as the lowest concentration at which the tested concentration fully prevents the visible growth of bacteria after a 24-hour incubation period at 37 °C, as measured by an ELISA reader. While, for determination of MBC, 10 µl from each well with concentrations equal to or greater than the MIC was sub-cultured on Muller-Hinton agar for 24 hours at 37 °C. The MBC is characterized as the concentration of diosmin that eliminates 99.9% of the introduced bacteria [24].

Evaluation of Anti-Biofilm Activity of Diosmin

Anti-biofilm activity was assessed using crystal violet and triphenyl tetrazolium chloride (TTC) viability assays [2].

Minimum Biofilm Inhibition Concentration

The effectiveness of diosmin in combating biofilms formed by MRSA strains was evaluated using the crystal violet method, as per the specified protocol. As for the MIC, the same procedure was followed in the 96-well plate, and the plate was incubated at 37 °C. After incubation for 24 hours, planktonic cells and loosely bound cells were washed off three times with sterile normal saline, and the plates were dried. Afterward, the biofilm was stained with 0.250 mL of 0.4% (w/v) crystal violet. To eliminate excess stain, the contents of the wells were discarded and subsequently washed twice with sterile normal saline and dried. 0.250 mL of 30 (v/v) glacial acetic acid was introduced to each well to facilitate the adherence of the biofilm to crystal violet for duration of 10 minutes and measured at 600 nm [24].

MBIC is characterized as the lowest concentration that demonstrates the most significant reduction in biofilm formation relative to the control. Conversely, the MBIC of diosmin necessary to inhibit biofilm formation by 50% is referred to as minimum biofilm inhibitory concentration of 50 ($MBIC_{50}$). The percentage inhibition was measured as % of inhibition = (control OD_{600} - treated OD_{600})/control OD_{600}) × 100.

Cell Viability Assay of Diosmin

The activity of diosmin on the cell viability of different MRSA strains within biofilm was assess by using TTC assay (2,3,5-triphenyl-tetrazolium chloride), as described previously in crystal violet and MIC methodology with some modifications [25]. After 24 hours, the well contents were discarded, washed with normal saline, and then dried. After that, 50 µL of 2% TTC was added to each well of 96-well microtiter plate and then incubated in a dark condition at 37°C and 150 rpm to allow reduction of TTC by metabolically active cells to formazan red dye. After five hours, the absorbance was recorded at 450 nm. The percentage of inhibition in MRSA strains viable cells was calculated in reference to the untreated control culture.

Statistical Analysis

Data are expressed as mean ± standard deviation. Statistical analysis was performed using SPSS software (version 25.0; SPSS Inc., Chicago, IL, USA). Comparisons among different groups were conducted using one-way analysis of variance, followed by Dunnett's post-hoc test using GraphPad Prism 7 software (San Diego, CA, USA). Statistical significance was defined as $p < 0.05$.

Table 2. MIC and MBC of diosmin against MRSA isolates

Isolate number	MIC	MBC
MRSA 2	1 mg/ml	2 mg/ml
MRSA 4	1 mg/ml	2 mg/ml
MRSA 6	1 mg/ml	2 mg/ml
MRSA 7	1 mg/ml	2 mg/ml
MRSA 9	1 mg/ml	2 mg/ml

Note. MIC: Minimum inhibitory concentration; MBC: Minimum bactericidal concentration; & MRSA: Methicillin-resistant *Staphylococcus aureus*

RESULTS

Evaluation of MIC & MBC of Diosmin

The antibacterial efficacy of diosmin against five MRSA clinical isolates (MRSA 2, MRSA 4, MRSA 6, MRSA 7, and MRSA 9) was assessed using the broth microdilution method. Diosmin exhibited a consistent MIC of 1.5 mg/mL across all tested strains, effectively preventing visible bacterial growth after 24 hours of incubation at 37 °C. The MBC was determined to be greater than 3 mg/mL for all isolates, indicating that diosmin bactericidal activity requires higher concentrations than its inhibitory effects (**Table 2**).

Anti-Biofilm Activity $MBIC_{50}$

The ability of diosmin to inhibit biofilm formation by MRSA strains was evaluated using the crystal violet staining assay, with concentrations ranging from 0.002 to 1.449 mg/mL. Diosmin demonstrated dose-dependent inhibition of biofilm formation across all isolates (**Figure 1**). At the highest concentration tested (1.449 mg/mL), significant reductions in biofilm biomass were observed, with inhibition percentages of 79% (MRSA 2), 58% (MRSA 4), 52% (MRSA 6), 58% (MRSA 7), and 70% (MRSA 9). However, for isolates 2, 4, 6, 7, and 9, diosmin exhibited $MBIC_{50}$ values of 0.0048 mg/ml, 0.0150 mg/ml, 0.012 mg/ml, 0.035 mg/ml, and 0.0177 mg/m, respectively. These results indicate that diosmin effectively disrupts biofilm formation, with MRSA 2 and MRSA 9 showing the highest susceptibility.

Effect of Diosmin on Cell Viability

To confirm that diosmin antibiofilm activity was not solely due to reduced bacterial growth, cell viability within MRSA biofilms was assessed using a TTC assay. Biofilms treated with diosmin concentrations at or above the MIC (1.449 mg/mL) showed significant reductions in viable cells. Specifically, at 1.449 mg/mL and 0.97 mg/mL, cell viability was reduced by 72.51% and 48.50%, respectively, compared to untreated controls (**Figure 2**). At lower concentrations (0.324-0.00005 mg/mL), no significant inhibition was observed, with over 90% of cells remaining viable. Consequently, concentrations of 0.324, 0.108, and 0.036 mg/mL were selected for further studies due to their minimal impact on cell viability. The negative control DMSO showed no antibiofilm activity.

DISCUSSION AND CONCLUSION

The accelerating prevalence of bacteria capable of withstanding multiple antimicrobial agents has emerged as a critical concern for modern healthcare systems, particularly due to the sustained clinical burden imposed by MRSA [26]. Ongoing challenges in antibiotic discovery and development have shifted research efforts toward non-conventional antimicrobial sources, including biologically active constituents of medicinal plants [27]. Diosmin, a citrus-derived flavonoid glycoside known for its antioxidant and anti-inflammatory effects, has been widely studied in cardiovascular and metabolic contexts [18]; however, its effectiveness against MRSA remains limited and requires further investigation [28].

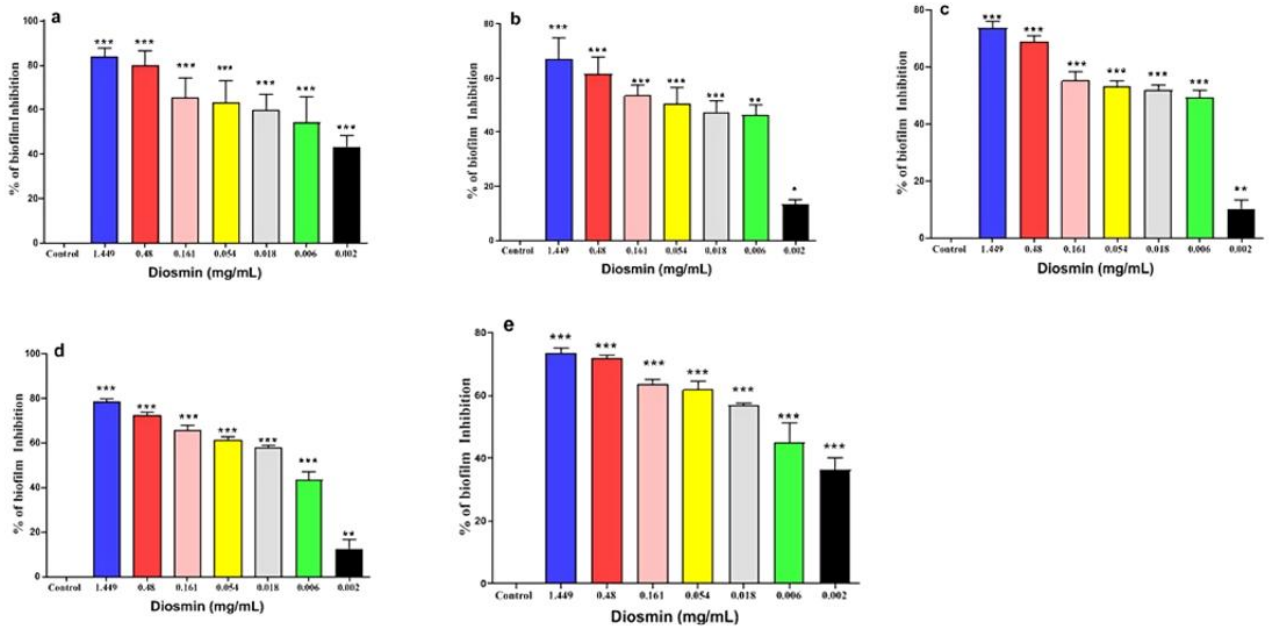

Figure 1. Antibiofilm effect of diosmin on different MRSA isolates (panels [2, 4, 6, 7, and 9] correspond to the five tested isolates: MRSA 2 [a], MRSA 4 [b], MRSA 6 [c], MRSA 7 [d], and MRSA 9 [e]); Biofilm formation was assessed using the crystal violet assay after 24 h of incubation with diosmin at concentrations ranging from 1.449 mg/mL to 0.002 mg/mL; Data are presented as mean ± standard deviation (n = 3); *$p < 0.05$; **$p < 0.01$; & ***$p < 0.001$ compared to control) (created by the authors using GraphPad Prism 7 software [San Diego, CA, USA])

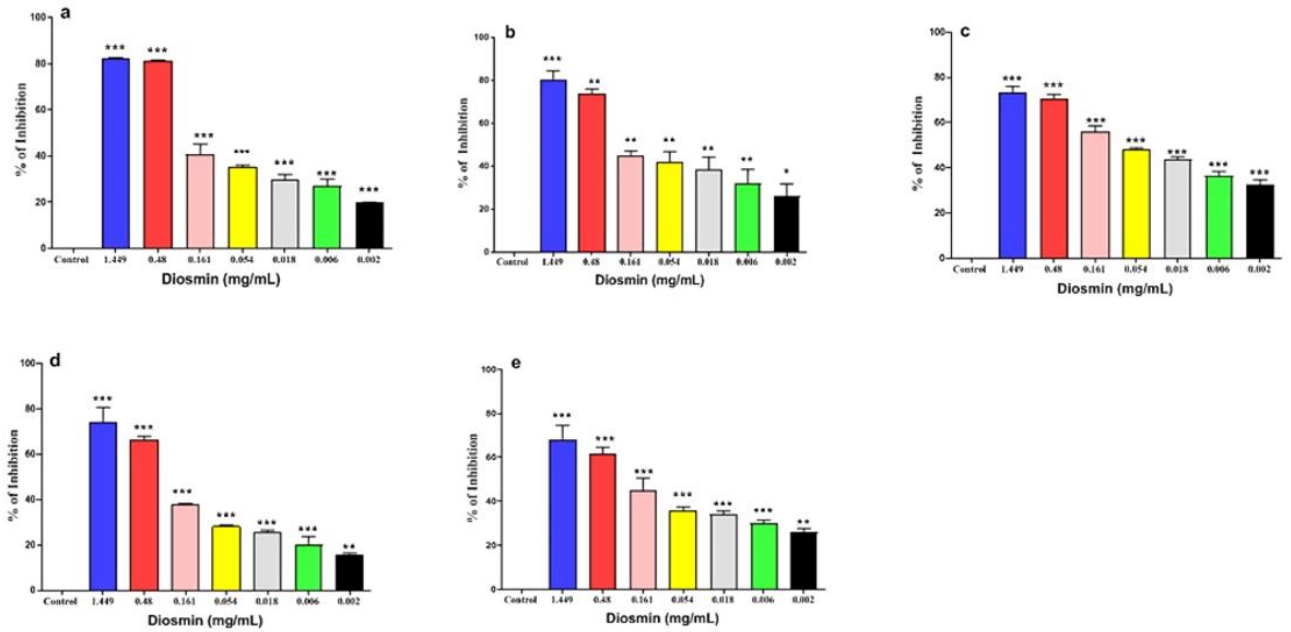

Figure 2. Percentage of inhibition in MRSA strains viable cells treated or untreated with diosmin (panels [2, 4, 6, 7, and 9] correspond to the five tested isolates: MRSA 2 [a], MRSA 4 [b], MRSA 6 [c], MRSA 7 [d], and MRSA 9 [e]); Cell viability of biofilm was assessed by using TTC assay after 24 h of incubation with diosmin at concentrations ranging from 1.449-0.002 mg/mL; Data are presented as mean ± standard deviation (n = 3); $p < 0.05$; $^{**}p < 0.01$, & $^{***}p < 0.001$ compared to control) (created by the authors using GraphPad Prism 7 software [San Diego, CA, USA])

This study shows that diosmin has significant antibacterial and antibiofilm activity against clinical MRSA isolates, suggesting its potential as a complementary approach for managing multidrug-resistant infections. The consistent MIC across isolates indicates a reliable inhibitory effect, while the higher MBC suggests a primarily bacteriostatic action at lower concentrations, requiring higher doses for bactericidal activity. This pattern is typical of flavonoids and supports their use as adjunct rather than standalone antimicrobial agents [26]. Diosmin demonstrated strong antibiofilm activity in a dose-dependent manner, with substantial reductions in biofilm biomass at higher concentrations. Biofilm-associated infections represent a major clinical challenge due to their inherent tolerance to antibiotics and host immune defenses [28].

The observed antibiofilm efficacy of diosmin is therefore particularly relevant, as it suggests an ability to interfere with early biofilm development and maturation, processes that are critical for persistent MRSA infections [29]. Assessment of cell viability within established biofilms using the TTC assay revealed that diosmin significantly reduced the metabolic activity of biofilm-embedded cells at concentrations equal to or exceeding the MIC. This finding indicates that, at higher concentrations, diosmin's antibiofilm activity is partly attributable to a direct inhibitory effect on bacterial viability within the biofilm matrix.

In contrast, sub-MIC concentrations showed minimal effects on cell viability, despite measurable reductions in biofilm formation. This observation suggests that diosmin may interfere with biofilm development through non-lethal mechanisms at lower doses [27]. Although the precise molecular mechanisms underlying diosmin's antibiofilm activity were not directly investigated in this study, several plausible explanations can be proposed based on the known biological properties of flavonoids. Previous studies on structurally related flavonoid compounds have shown that they can disrupt quorum sensing systems, reduce extracellular polymeric substance production, and interfere with bacterial surface adhesion [26]. It is therefore reasonable to hypothesize that diosmin may modulate similar pathways, thereby weakening biofilm structure and stability without exerting overt cytotoxic effects at sub-inhibitory concentrations. These non-lethal antibiofilm actions are particularly attractive, as they may reduce selective pressure for resistance development [27]. Despite its promising antibiofilm and antibacterial effects, the relatively high MBC values observed indicate that diosmin alone may not be sufficient for complete bacterial eradication at clinically feasible concentrations. This limitation reinforces the potential value of combination strategies, where diosmin could be used alongside conventional antibiotics to enhance overall efficacy, improve biofilm penetration, and possibly reduce required antibiotic doses [30]. In summary, diosmin shows promise as an antibacterial and antibiofilm agent against MRSA, particularly as an adjunct therapy. Future studies should clarify its molecular targets, assess synergy with antibiotics, and confirm its efficacy and safety in vivo to establish its clinical relevance against resistant staphylococcal infections.

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Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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