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Monocarbonyl Curcuminoids with Improved Stability as Antibacterial Agents against *Staphylococcus aureus* and Their Mechanistic Studies

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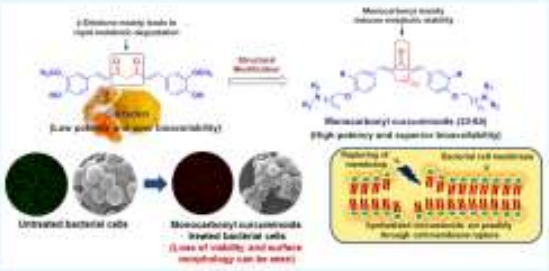
Supporting Information

ABSTRACT: Curcumin has been known to possess diverse pharmacological effects at relatively nontoxic doses; however, its therapeutic potential is severely restricted because of its low aqueous solubility and poor stability under physiological conditions. To overcome its limitations, we had previously designed several monocarbonyl curcuminoids by modifying the central β-diketone moiety of curcumin. In this study, the antibacterial activity of 33 curcuminoids from this designed library has been screened, six of which displayed potent antibacterial activity against clinically relevant *Staphylococcus aureus*. These curcuminoids were found to be very stable at physiological conditions and did not cause any toxicity toward mammalian cells. Mechanistically, out of these six curcuminoids, five caused instant membrane depolarization and were able to permeabilize the bacterial membrane, which could be the reason for their potent bactericidal activity and the sixth one killed staphylococcal cells without damaging the bacterial membrane. Overall, the present work established the staphylocidal potency of six water-soluble, nontoxic curcuminoids, thereby providing an impetus for the development of these lead curcuminoids for therapeutic use against *S. aureus*.



1. INTRODUCTION

Staphylococcus aureus (*S. aureus*) is an opportunistic pathogen and a commensal colonizer of nasal carriage and skin in approximately 30% of the world population.[1] Its carriers are at higher risk of infection, as colonization provides a reservoir for *S. aureus* and when host defenses are breached, it becomes a clinically significant pathogen and causes a wide spectrum of diseases, from skin and soft tissue infections, such as abscesses, carbuncles, and cellulitis to life-threatening conditions, such as bacteraemia, osteomyelitis, meningitis, pneumonia, endocarditis, and urinary tract infections.[2,3] Due to frequent and indiscriminate use of antibiotics, the frequency of both hospital-acquired and community-acquired infections has increased significantly in last few decades.[4] This increased prevalence of infections has been associated with the emergence of resistant strains, mainly, vancomycin-resistant *S. aureus* strains and methicillin-resistant *S. aureus*.[5,6] Many clinically isolated *S. aureus* are now considered as multiple drug-resistant (MDR) bacteria as they showed resistance toward many available drugs.[7] These resistant strains continue to parade higher mortality and morbidity in many developing as well as developed countries.[8,9] There is a major deficit of effective treatment against its infection and demands an urgent need to search for alternatives. Since a long time, plant-based active compounds (such as phenols, quinones, alkaloids, and other secondary metabolites) have been explored for discovering new compounds and still gain much attention.[10] Among such natural compounds, curcumin is one of the most studied polyphenolic compounds, which targets various metabolic pathways in the biological system.[11]

Curcumin is a yellow polyphenolic compound obtained from the rhizomes of the perennial plant turmeric (*Curcuma longa*). Besides its well-known use as food coloring spice, it has also been used for the treatment of wound healing, burns, common cold, fever, arthritis, and liver disorders since ancient times in many Asian countries.[12] Numerous studies in the last few decades have explored the diverse pharmacological properties of curcumin, which include antioxidant, anti-inflammatory,[13] antiviral,[14] and antibacterial activities[15] and have shown promising therapeutic utility against various neurodegenerative diseases.[16] The excellent potency of curcumin was associated with its safe toxicity profile and it

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