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Curcumin and Its Analogues: Potent Natural Antibacterial Compounds against Staphylococcus aureus

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Abstract : Staphylococcus aureus is the most pathogenic of all staphylococci, a major cause of nosocomial infections, and known for acquiring resistance towards various commonly used antibiotics. Due to the widespread use of synthetic drugs, clinicians are now facing a serious threat in healthcare. The increasing resistance in staphylococci has created a need for alternatives to these synthetic drugs. One of the alternatives is a natural plant-based medicine for both disease prevention as well as the treatment of chronic diseases. Among such natural compounds, curcumin is one of the most studied molecules and has been an integral part of traditional medicines and Ayurveda from ancient times. It is a natural polyphenolic compound with diverse pharmacological effects, including anti-inflammatory, antioxidant, anti-cancerous and antibacterial activities. In spite of its efficacy and potential, curcumin has not been approved as a therapeutic agent yet, because of its low solubility, low bioavailability, and rapid metabolism in vivo. The presence of central β-diketone moiety in curcumin is responsible for its rapid metabolism. To overcome this, in the present study, curcuminoids were designed by modifying the central β-diketone moiety of curcumin into mono carbonyl moiety and their antibacterial potency against S. aureus ATCC 29213 was determined. Further, the mode of action and hemolytic activity of the most potent curcuminoids were studied. Minimum inhibitory concentration (MIC) and in vitro killing kinetics were used to study the antibacterial activity of the designed curcuminoids. For hemolytic assay, mouse Red blood cells were incubated with curcuminoids and hemoglobin release was measured spectrophotometrically. The mode of action of curcuminoids was analysed by membrane depolarization assay using membrane potential sensitive dye 3,3'-dipropylthiacarbocyanine iodide (DiSC3(5)) through spectrofluorimetry and membrane permeabilization assay using calcein-AM through flow cytometry. Antibacterial screening of the designed library (61 curcuminoids) revealed excellent in vitro potency of six compounds against S. aureus (MIC 8 to 32 µg/ml). Moreover, these six compounds were found to be non-hemolytic up to 225 µg/ml that is much higher than their corresponding MIC values. The in vitro killing kinetics data showed five of these lead compounds to be bactericidal causing >3 log reduction in the viable cell count within 4 hrs at 5 × MIC while the sixth compound was found to be bacteriostatic. Depolarization assay revealed that all the six curcuminoids caused depolarization in their corresponding MIC range. Further, the membrane permeabilization assay showed that all the six curcuminoids caused permeabilization at 5 × MIC in 2 hrs. This membrane depolarization and permeabilization caused by curcuminoids found to be in correlation with their corresponding killing efficacy. Both these assays point out that membrane perturbations might be a primary mode of action for these curcuminoids. Overall, the present study leads us six water soluble, non-hemolytic, membrane-active curcuminoids and provided an impetus for further research on therapeutic use of these lead curcuminoids against S. aureus.

Keywords : antibacterial, curcumin, minimum inhibitory concentration , Staphylococcus aureus
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