

## Publication

## Antimicrobial properties of 8-hydroxyserrulat-14-en-19-oic acid for treatment of implant-associated infections

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Treatment options are limited for implant-associated infections (IAI) that are mainly caused by biofilm-forming staphylococci. We report here on the activity of the serrulatane compound 8-hydroxyserrulat-14-en-19-oic acid (EN4), a diterpene isolated from the Australian plant *Eremophila neglecta*. EN4 elicited antimicrobial activity toward various Gram-positive bacteria but not to Gram-negative bacteria. It showed a similar bactericidal effect against logarithmic-phase, stationary-phase, and adherent *Staphylococcus epidermidis*, as well as against methicillin-susceptible and methicillin-resistant *S. aureus* with MICs of 25 to 50 µg/ml and MBCs of 50 to 100 µg/ml. The bactericidal activity of EN4 was similar against *S. epidermidis* and its Deltaica mutant, which is unable to produce polysaccharide intercellular adhesin-mediated biofilm. In time-kill studies, EN4 exhibited a rapid and concentration-dependent killing of staphylococci, reducing bacterial counts by >3 log(10) CFU/ml within 5 min at concentrations of >50 µg/ml. Investigation of the mode of action of EN4 revealed membranolytic properties and a general inhibition of macromolecular biosynthesis, suggesting a multitarget activity. In vitro-tested cytotoxicity on eukaryotic cells was time and concentration dependent in the range of the MBCs. EN4 was then tested in a mouse tissue cage model, where it showed neither bactericidal nor cytotoxic effects, indicating an inhibition of its activity. Inhibition assays revealed that this was caused by interactions with albumin. Overall, these findings suggest that, upon structural changes, EN4 might be a promising pharmacophore for the development of new antimicrobials to treat IAI.

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