10th Brazilian Conference on Natural Products
XXXVI RESEM
4-7 November 2025, Belo Horizonte, MG, Brazil
Section: 03

PHLOROGLUCINOLS FROM *Melaleuca viminalis*: DEREPLICATION, ISOLATION AND ANTIMICROBIAL ACTIVITY AGAINST METHICILLIN-RESISTANT *Staphylococcus aureus*

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Staphylococcus aureus is a Gram-positive bacterium classified among the ESKAPE pathogens, recognized for its high prevalence in hospital settings and its increasing resistance to multiple drugs, particularly methicillin. This resilience is largely due to its efficient adaptive mechanisms against conventional antibiotic therapies. In this context, the search for alternative compounds capable of inhibiting its survival and pathogenicity is urgent. CEPID-ARIES has been dedicated to the discovery of natural products with potential to counteract microbial resistance[1]. Among the plant species of interest, *Melaleuca viminalis* (Myrtaceae) stands out for its diverse classes of secondary metabolites, especially phloroglucinols—compounds with remarkable structural diversity, including bicyclic, tricyclic, and other frameworks—and relevant biological potential. Previous studies have reported antimicrobial activity of phloroglucinols isolated from *M. viminalis* against both Gram-positive and Gram-negative bacteria[2]. Considering the increasing dissemination of resistant bacterial strains, this study aimed to perform the dereplication of compounds from the dichloromethane phase fraction by LC-MS/MS integrating the data obtained into the GNPS2 platform and to evaluate their antimicrobial activity against two *S. aureus* strains: ATCC Sa29213 (susceptible to several antimicrobials, including oxacillin) and MRSA Sa43300 (methicillin-resistant), followed by isolation via HPLC. GNPS2 analysis revealed a cluster with fragmentation patterns consistent with phloroglucinols. Subsequent isolation and characterization enabled the manual annotation of three compounds: 2,6-dihydroxy-4-methoxyisovalerophenone, Aspidinol C, and Pulverulentone. In antimicrobial assays, the fraction exhibited inhibition zones of 10.6 mm (Sa29213) and 16.8 mm (Sa43300). The Minimum Inhibitory Concentration values were >64 µg/mL for the sensitive strain and 32 µg/mL for the resistant strain. These findings highlight the promising antimicrobial potential of phloroglucinols from this fraction, particularly against methicillin-resistant *S. aureus*, and underscore their relevance as candidates for future pharmacological investigations. In light of these results, the isolated compounds may be tested to assess their non-synergistic potential.

Keywords: *Phloroglucinols, Dereplication, GNPS2, Antimicrobial Activity, Staphylococcus aureus.*

[1]CEPID-ARIES - Antimicrobial Resistance Institute of São Paulo (FAPESP 2021/10599-3) (https://site.unifesp.br/cepidaries/)

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