ABSTRACT

Ethnopharmacological relevance: Warburgia ugandensis Sprague subspecies ugandensis is a plant widely distributed in Eastern, Central and Southern Africa. In humans, it is used to treat respiratory infections, tooth aches, malaria, skin infections, venereal diseases, diarrhea, fevers and aches.

Aim of the study: This study aims to identify the bioactive compounds against clinically important biofilm-forming strains of Candida and staphylococci that are responsible for tissue and implanted device-related infections.

Methods: Using a bioassay-guided fractionation approach, hexane -, ethanol -, acetone - and water extracts from the leaves of W. ugandensis, their subsequent fractions and isolated compounds were tested against both developing and preformed 24 h-biofilms of Candida albicans SC5314, Candida glabrata BG2, Candida glabrata ATCC 2001, Staphylococcus epidermidis 1457 and Staphylococcus aureus USA 300 using microtiter susceptibility tests. Planktonic cells were also tested in parallel for comparison purposes. Confocal scanning laser microscopy was also used to visualize effects of isolated compounds on biofilm formation.

Results: Warburganal, polygodial and alpha-linolenic acid (ALA) were the major bioactive compounds isolated from the acetone extract of W. ugandensis. For both warburganal and polygodial, the biofilm inhibitory concentration that inhibits 50% of C. albicans developing biofilms (BIC_{50}) was 4.5 ± 1 and 10.8 ± 5 µg/mL respectively. Against S. aureus developing biofilms, this value was 37.9 ± 8 µg/mL and 25 µg/mL with warburganal and ALA respectively. Eradication of preformed 24 h biofilms was also observed. Interestingly, synergy between the sesquiterpenoids and azoles against developing C. albicans biofilms resulted in an approximately ten-fold decrease of the effective concentration required to completely inhibit growth of the biofilms by individual compounds. The hydroxyl group in position C-9 in warburganal was identified as essential for activity against staphylococcal biofilms. We also identified additional promising bioactive sesquiterpenoids; drimenol and drimendiol from the structure-activity relationship (SAR) studies.

Conclusions: ALA and four sesquiterpenoids: polygodial, warburganal, drimenol and drimendiol, have shown biofilm-inhibitory activity that has not been reported before and is worth following up. These compounds are potential drug candidates to manage biofilm-based infections, possibly in combination with azoles.

Keywords: Azoles; Chromatography; Multi-drug resistance; Sesquiterpenoids; Synergy; W. ugandensis.