ABSTRACT

Indonesia has an astounding biodiversity, including marine biodiversity. The waters surrounding Indonesia are home to a variety of interesting creatures known as marine sponges. These sponges are known for their unique chemical defense mechanisms due to a lack in mobility that could be harnessed for a plethora of potentially useful medical applications. These organisms can also produce promising novel antifungal agents, such as aaptamines produced by *Aaptos aaptos*. This study will explore Indonesian marine sponge extracts and sponge-associated microbiome extracts as potential sources of novel fungal efflux pump inhibitors of *Candida glabrata* Cdr1 and Pdh1. *C. glabrata* is known for its resistance to azole antifungals and its prevalence in mucosal and systemic candidosis. Resistance often arises due to the overexpression of efflux pump transporters, which actively expel azoles out of the cell. Major efflux transporters, such as *C. glabrata* Cdr1 (*CgCDR1*) and Pdh1 (*CgPDH1*), that belong to the ATP-binding cassette (ABC) family are implicated in azole resistance. However, inhibitors of these transporters could be used in combination with existing azole antifungals to successfully treat candidosis cases caused by *C. glabrata* infections. This study will employ liquid microdilution, disk diffusion, and fluconazole chemosensitization assays with *Saccharomyces cerevisiae* cells overexpressing *CgCDR1* and *CgPDH1*. This study also employs medicinal chemistry analysis by combining liquid chromatography with high resolution mass spectrometry (LC-HRMS) and molecular docking experiments. This study highlights the tremendous potential of Indonesian marine sponge extracts as a source for novel antifungals, including novel efflux pump inhibitors.

Keywords: Azole resistance, *Candida* glabrata, CDR1, efflux pump, marine sponge, PDH1