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ORIGINAL ARTICLE

Natural trypanocidal product produced by endophytic fungi through co-culturing

Jainara Santos do Nascimento[1] · Felipe Moura Silva[1] · Cynthia Alejandra Magallanes-Noguera[2] · Marcela Kurina-Sanz[2] · Elda Gonçalves dos Santos[3] · Ivo Santana Caldas[3] · Jaine Honorata Hortolan Luiz[4] · Eliane de Oliveira Silva[1]

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Abstract
Endophytic fungi live inside vegetal tissues without causing damage to the host plant and may provide lead compounds for drug discovery. The co-culture of two or more endophytic fungi can trigger silent gene clusters, which could lead to the isolation of bioactive compounds. In this study, two endophytic strains isolated from *Handroanthus impetiginosus* leaves, identified as *Talaromyces purpurogenus* H4 and *Phanerochaete* sp. H2, were grown in mixed and axenic cultures. The meroterpenoid austin was detected only in the extracts from the mixed culture. Once isolated, austin displayed very interesting trypanocidal activity, with an IC_{50} value of 36.6 ± 1.2 μg/mL against *Trypanosoma cruzi* in the epimastigote form. The results obtained highlight the importance of the co-culturing of endophytic fungi to obtain natural bioactive products. The findings also enhance our understanding of the ecological relationships between endophytic fungi.

Introduction

The group designated as neglected tropical diseases (NTDs) includes, among other parasitic illnesses, Chagas disease, which is caused by the protozoan parasite *Trypanosoma cruzi*. The World Health Organization has reported that 8 million people are infected by *T. cruzi* worldwide, mostly in Latin America, and Chagas disease causes around 10,000 deaths per year. The main drugs currently used in the treatment of Chagas disease during the acute phase are nifurtimox and benznidazole, which have been used for more than three decades. However, these drugs have low efficacy and cause serious side effects in patients (WHO 2018).

Secondary metabolites currently play a crucial role in the search for new lead compounds (Cragg and Newman 2013). Due to the ubiquitous occurrence of microorganisms, along with the wide chemodiversity that can occur within a given species (Bertrand et al. 2014), they are interesting sources of natural bioactive scaffolds (Demain 2014). In this context, the endophytic fungi merit attention (de Carvalho et al. 2016; Silva et al. 2017). Endophytic microorganisms naturally occur in vegetal tissue, without causing notable damage to the host plant (Arnold and Lutzoni 2007). Several studies have provided evidence that the interaction between endophytic community members can play a major role in the onset of metabolite production, such as the biosynthesis of defense metabolites and quorum-sensing signals (Akone et al. 2016).

The genes encoding these biosynthetic pathways are usually clustered (Yamanaka et al. 2014). In many cases, they are not expressed under standard laboratory culture conditions because their activation relies on environmental cues and, therefore, only a minority of the potential secondary metabolites can be investigated in vitro (Scherlach and Hertweck 2009).

Silenced biosynthesis pathways, mainly those related to defense compounds, may be activated when the microbes are grown together in co-cultures or in confrontation

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✉ Eliane de Oliveira Silva
elianeos@ufba.br

[1] Organic Chemistry Department, Chemistry Institute, Federal University of Bahia, Barão de Jeremoabo, Salvador, Bahia 40170-115, Brazil

[2] INTEQUI-CONICET, Facultad de Química, Bioquímica y Farmacia, Universidad Nacional de San Luis, San Luis, Argentina

[3] Pathology and Parasitology Department, Institute of Biomedical Sciences, Federal University of Alfenas, Alfenas, Brazil

[4] Chemistry Institute, Federal University of Alfenas, Alfenas, Brazil

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