

TITLE: Endophytic fungus *Sordaria spp* as a source of new substances with antimycobacterial and anti-inflammatory potential

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ABSTRACT:

The emergence of multidrug-resistant *M. tuberculosis (Mtb)* strains is a threat to tuberculosis (TB) control worldwide. Additionally, the non-tuberculous mycobacteria which are able to cause TB-like pulmonary infections, such as *M. kansasii (Mkan)*, frequently display resistance to antibiotics as well. Severe pulmonary infections caused by these strains are often associated with exacerbated lung inflammation leading to necrotic pathology and formation of cavities, that encourages the use of adjuvant anti-inflammatory therapy in addition to anti-TB chemotherapy. Recently, we described a new approach for the search for new natural or synthetic substances combining anti-inflammatory and antimycobacterial properties. In this work, we evaluated the natural products of the endophytic fungus *Sordaria spp*, isolated from *Tocoyena bullata*, for the dual activity: suppression of *Mtb* or *Mkan* growth and inhibition of macrophage proinflammatory activation. Suspensions of BCG, *Mtb* H37Rv and *Mkan* (strains 12478/ATCC, 4404 and 8835) in culture medium were incubated with crude extracts of the endophytic fungus (4-500 µg/ml) for 5 days. LPS-stimulated RAW 264.7 macrophages were incubated with the same samples for 24 hours to evaluate the capacity to inhibit production of inflammatory mediators (NO, TNF-α and PGE₂) and the cytotoxicity. All samples were able to inhibit propagation of the studied strains. The MIC₅₀ value of the ethanolic extract against *M. bovis* BCG and *Mtb* H37Rv was 1,5±0,6, and 66,8±0,1, respectively, and the values for *Mkan* strains 12478, 4404 e 8835 varied between MIC₅₀ 0,4±0,6 and 3,4±1,0. The fraction in AcOEt was less active against the *Mkan* strains (MIC₅₀ 20,9±0,8 - 23,0±0,8) and the *Mtb* H37Rv strain (MIC₅₀ 84,8±1,9). Lasiodiplodin, a substance isolated from the extract, inhibited the growth of all strains, emphasizing *M. bovis* BCG (MIC₅₀ 6,7±0,3). The samples exhibited the anti-inflammatory activity as well, inhibiting more than 80% of NO production, IC₅₀ 77,2±2,2 (extract), IC₅₀ 33,8±0,2 (AcOEt). Importantly, the samples were not cytotoxic for macrophages in the used concentrations. Lasiodiplodin was the most active compound in inhibiting the production of TNF-α (IC₅₀ 17,3±0,7), whereas the extract was the most active in inhibiting the production of PGE₂ (IC₅₀ 93,5±0,8). In conclusion, the substances isolated from fungus *Sordaria* are promising for the discovery of new drugs for the treatment of severe pulmonary infections caused by *Mtb* and *Mkas*.

Keywords: Tuberculosis, natural products, Endophytic fungus

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