Lavandula angustifolia essential oil induces oxidative stress, stiffening of membranes, and cell wall in Cryptococcus spp.

Yohana Porto Calegari Alves[1], Rafael Lopes da Rosa[1], Renata Pereira Costa[1], Camila Innocente Alves[1], Aline Martins Faustino[1], John R. Yates III[2], Walter Orlando Beys-da-Silva[1], Lucélia Santi[1]

[1.] UFRGS, Universidade Federal do Rio Grande do Sul, Av. Ipiranga, 2752 - Azenha, Porto Alegre - RS, 90610-000;
[2.] Scripps Research, Scripps Research , La Jolla, CA, 92122, United States;

Cryptococcosis is considered a global public health problem, with *Cryptococcus* sp. being the most lethal fungus in humans due to treatment limitations. In view of this, it is extremely important to carry out studies focused on discovering promising antifungal agents, exploring the immense potential of natural resources in the plant kingdom for this purpose.With advances in technological research, proteomics has made it possible to profile proteins and molecular networks, thereby discovering biological markers and targets for new medicines. Although some studies have already demonstrated the antifungal effect of *Lavandula angustifolia* essential oil (LEO) or its main components on other microorganisms, this is the first report, at a molecular level, of the exposure of *Cryptococcus neoformans* and *Cryptococcus deuterogattii* to LEO. In this work, we evaluated the molecular changes induced by the exposure of *C. neoformans* (strain H99) and *C. deuterogattii* (strain R265) to LEO using a proteomic approach. Cells treated or not (control) with ½ MIC of LEO were lyophilized, disrupted with liquid nitrogen, and suspended in a digestion buffer. Protein digestion was subjected to mass spectrometry using the MudPIT technique (multidimensional protein identification technology), with protein identification and quantification analysis performed using the Integrated Proteomics Pipeline (IP2). PatternLab software was used to identify unique and differentially expressed proteins, and the Blast2GO tool was used to categorize detected proteins in Gene Ontology (GO) and the KEGG mapping module. To validate the results obtained, ROS quantification experiments, cell extravasation assay, cellular measurements for C. neoformans, and fluorescence microscopy for C. deuterogattii were carried out. Our findings indicate that LEO creates a stressful environment in both strains, as observed by the expression of proteins involved in catabolic processes and oxidoreductase activity in *C. neoformans*, and proteins involved in stress in *C. deuterogattii*. However, the response to this stimulus differs between the two species. Our proteomic data indicate broad changes in metabolic processes, stress responses, and cellular architecture. In *C. neoformans*, we observed changes in energy metabolism, impairment in mitochondria, and pathways associated with alternative energy sources and response to oxidative stress. On the other hand, in *C. deuterogattii*, changes were detected in pathways related to cellular architecture, suggesting morphological changes such as membrane and cell wall stiffening. We highlight the importance of understanding the molecular changes caused by LEO in *C. neoformans* and *C. deuterorogattii* when searching for new antifungal agents, which are urgently needed.

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