Effects of Plant Extracts on Pdr5p from Yeast - A new hope to solve the multidrug resistance phenotype?

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Fungal resistance to drugs used in therapy is a very common problem, and the most preoccupying phenomenon is the multidrug resistance. This kind of resistance is promoted by transporter proteins from the ABC (ATP Binding Cassette) superfamily. In *Saccharomyces cerevisiae*, ABC protein family comprises 31 genes. The best characterized yeast ABC transporter is Pdr5p, which confers resistance to compounds like antifungal and anticancer drugs and is homologue to other transporters from pathogenic fungi, as well as mammalian P-glycoprotein. In this work, we have evaluated the effect of 43 Brazilian plant extracts on Pdr5p ATPase activity. Our results indicate that some of the compounds present in the species tested may act as Pdr5p inhibitors, as we have found up to 72% of inhibition, depending on the plant extract used. The best results were obtained with the following plants: *Bauhinia microstachya* var. *microstachya* (Fabaceae), *Astronium fraxinifolium* (Anacardiaceae), *Croton foribundus* (Euphorbiaceae), *Brosimum guianense* (Moraceae), *Sparattosperma leucanthum* (Bignoniaceae), *Luehia grandiflora* (Tiliaceae), *Aparisthmium cordatum* (Euphorbiaceae), *Pera heteranthera* (Euphorbiaceae), *Bauhinia microstachya* var. *massambabensis* (Fabaceae), *Dalbergia nigra* (Fabaceae), *Bathysa australis* (Rubiaceae), *Melanoxylon brauna* (Fabaceae), *Mabea fistulifera* (Euphorbiaceae) and *Virola oleifera* (Myristicaceae). Five of these extracts with the lower IC_{50} values, were selected for a partitioning against solvents of growing polarities (hexane, dichloromethane, ethyl acetate and buthanol) and these new products were tested on Pdr5p ATPase activity. Except for the partition against buthanol from *Bathysa australis* extract, all the other partitions presented lower or equal inhibition values to their ethanolic extracts. The ethyl acetate partitions of the *Mabea fistulifera* and *Bauhinia microstachya* var. *massambabensis* extracts were submitted to chromatographic techniques, in order to isolate the active compounds. The fractions obtained were tested against Pdr5p ATPase activity and selected for new purification steps. We were able to isolate from the *Mabea fistulifera* extract gallic acid (IC_{50} ~ 185µg/mL), which was not known to inhibit the enzyme Pdr5p. Although not suitable for clinical use, for its knows toxicity, this compound can be used for the elucidation of Pdr5p's structure and function, as it has been shown that its inhibition of ATPase activity occurs in a competitive way for the Nucleotide Binding Site (NBD).

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