The role of quinones as inhibitors of respiratory chain and redox metabolism in *Leishmania infantum*

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Quinones may induce redox cycle and oxidative stress or act as inhibitors of mitochondrial respiratory complexes. In this present study, we evaluated new naphthoquinones (LQBs) for their ability to induce mitochondrial changes in *L. infantum* and to inhibit complexes I, II or III of isolated mitochondria from murine liver. LQBs showed good leishmanicidal activity with IC_{50} less than 2.5 µM and IC_{90} less than 4 µM. All prototypes altered the parasite mitochondrial activity by accelerating reduction of resazurin and induced changes in mitochondrial membrane potential ($\Delta\Psi m$). LQBs 149, 168, 182, 187, 222 and 236 also induced a significant increase in ROS production. In addition, we evaluated the respiratory activity on intact parasites in oxygraph. However, no significant changes were induced by any of the evaluated prototypes. The intracellular redox control in trypanosomatids is based on trypanothione reductase (TR), an important enzyme for the detoxification of ROS. LQBs also demonstrated the ability to inhibit the activity of TR. In an attempt to elucidate the selectivity of these substances, we assayed the activity of mitochondrial complexes isolated from murine liver. Our results suggest that LQBs 18, 32 and 168 may be inhibiting the complex I, LQBs 149 and 222 the complex II, the LQB 182 and 236 complexes III or IV and LQB 187 complex III in the highest concentrations. We conclude that all LQBs have the ability to induce mitochondrial changes in the parasite, though the mechanism of action on the parasite remains to be elucidated.

Keywords: Quinones; *Leishmania*; mitochondria