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# Neuroprotective effects of mitochondria-targeted antioxidants in a Parkinson's disease *in vitro* model

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## Abstract

**Background:** Parkinson's disease (PD) is a neurodegenerative disease with early prominent death of dopaminergic neurons in the *substantia nigra pars compacta*, concurrently with Lewys body formation, iron accumulation, oxidative stress and ferroptosis[1–3]. Since there is no effective therapy capable of stopping/delaying disease progression, phenolic acids such as hydroxycinnamic and hydroxybenzoic acids (HCA and HBA, respectively), and their derivatives, are being extensively explored to target oxidative stress and iron overload, pathophysiological mechanisms involved in PD[4–6]. **Objective:** The main objective of this work was to evaluate, *in vitro*, the potential neuroprotective effects of a series of mitochondriotropic antioxidants (HCA and HBA derivatives) against iron overload and ferroptosis, mechanisms involved in PD pathophysiology. **Methods:** Differentiated SH-SY5Y cells were used as *in vitro* model and compounds (0–100 µM) cytotoxicity evaluated, 24h after exposure, by the neutral red uptake and resazurin reduction assays, to select non-cytotoxic concentrations. To evaluate the compounds' neuroprotective effects, two chemical aggressors were used, Fe(III) (500 and 1000 µM, to mimic iron overload) and erastin (20 and 40 µM, a ferroptosis inducer). The cytotoxicity of the chemical aggressors was evaluated by the NR uptake assay 24h after exposure to the oxidative insults in the presence and absence of the mitochondriotropic antioxidants (10 and 50 µM, non-cytotoxic concentrations). The potential neuroprotective effects against the combination of the two chemical aggressors was also evaluated [100 µM Fe(III) + 2 µM erastin]. **Results:** Ten of the 11 compounds significantly reduced Fe(III)-induced cell death, while seven compounds afforded a significant protection against erastin-induced cytotoxicity. Regarding the simultaneous exposure to Fe(III) and erastin (where only compounds that were neuroprotective against both the aggressors alone were tested), all the five compounds selected demonstrated significant neuroprotective effects. **Conclusions:** Although preliminary, these results clearly demonstrated the potential neuroprotective effects of these compounds, open a new perspective for PD treatment.

**Keywords:** Parkinson's disease; neuroprotection; mitochondriotropic antioxidants; disease-modifying drugs

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