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Polyphenolic extract of *Euphorbia supina* attenuates manganese-induced neurotoxicity by enhancing antioxidant activity through regulation of ER stress and ER stress-mediated apoptosis *in vitro* and *in vivo*

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This study is aimed to investigate the protective role of polyphenolic extract of *Euphorbia supina* (PPEES) on Mn-induced neurotoxicity and the underlying mechanism in human neuroblastoma SK-N-MC cells and Sprague-Dawley (SD) male rat brain. PPEES possessed significant amount of total phenolic and flavonoid contents. PPEES also showed significant antioxidant activity in 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging and reducing power capacity (RPC) assays. Our results showed that Mn treatment significantly reduced cell viability and increased lactate dehydrogenase (LDH) level, which was attenuated by PPEES pretreatment at 100 and 200 g/mL. Additionally, PPEES pretreatment markedly attenuated Mn-induced antioxidant status alteration by resolving the ROS, MDA and GSH levels and SOD and CAT activities. PPEES pretreatment also significantly attenuated Mn-induced mitochondrial membrane potential (DYm) and apoptosis. Meanwhile, PPEES pretreatment significantly reversed the Mn-induced alteration in the GRP78, GADD34, XBP-1, CHOP, Bcl-2, Bax and caspase-3 activities. Furthermore, administration of PPEES (100 and 200 mg/kg) to Mn exposed rats showed improvement of histopathological alteration in comparison to Mn-treated rats. Moreover, administration of PPEES to Mn exposed rats showed significant reduction of 8-OHdG and Bax immunoreactivity. The results suggest that PPEES treatment reduces Mn-induced oxidative stress and neuronal cell loss in SK-N-MC cells and in the rat brain. Therefore, PPEES may be considered as potential treatment in Mn-intoxicated patients.

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