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Thymoquinone prevents neurodegeneration against MPTP *in vivo* model of Parkinson's disease and modulates α-synuclein aggregation *in vitro*

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Parkinson's disease (PD) is a common neurodegenerative disease, characterized by progressive dopaminergic neurodegeneration with concomitant increase in oxidative stress and subsequent neuroinflammation in the substantia nigra pars compacta (SNc) of the midbrain. Studies are currently focusing on targeting neuroinflammation and oxidative stress to effectively treat PD. This study evaluated the neuroprotective effect of TQ, one of the active compounds in the black seed, against 1-methyl-4-phenyl 1,2,3,6 tetrahydropyridine (MPTP)-induced PD mouse model. Here, TQ treatment for 1 week (dose, 10 mg/kg *b. wt.)* prior to MPTP (25 mg/kg *b. wt.*) was performed. MPTP administration caused decreased activities of superoxide dismutase, catalase and depletion of reduced glutathione, with a concomitant rise in the lipid peroxidation product. It significantly increased pro-inflammatory cytokines and elevated inflammatory mediators such as COX-2 and iNOS in the striatum. Immunohistochemical analysis revealed dopamine neuron loss in the SNc area and decreased dopamine transporters in the striatum following MPTP administration. However, TQ treatment significantly rescued dopaminergic neuronal loss and dopamine transporters. TQ treatment further prevented glutathione depletion, inhibited lipid peroxidation, and attenuated pro-inflammatory cytokines. TQ also reduced the increased levels of inflammatory mediators, such as COX-2 and iNOS. *In vitro* analysis found that TQ significantly inhibits α-synuclein aggregation and prevents cell death induced by pre-formed fibrils. Thus, TQ not only scavenges the MPTP-induced toxicity but also prevents α-synuclein-fibril formation and associated toxicity.

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