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The Neuroprotective Capacity of Flavones from Africa Plants and from a Nanosomal Quercetin Preparation

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The high morbidity, high socioeconomic costs and lack of specific treatments are key factors that define the relevance of brain pathology for human health and the importance of research on neuronal protective agents. Epidemiological studies have shown beneficial effects of flavonoids on arteriosclerosis-related pathology in general and neurodegeneration in particular.

We have demonstrated that quercetin and structurally related flavonoids show a marked protective capacity in *in vitro* experimental conditions such as that induced by medium concentrations of H_2O_2 added to PC12 cells or cerebellar granular neurons in culture.
We evaluated the protective capacity of 13 flavones structurally related to quercetin, isolated from Kenyan plants, to rescue primary cerebellar granule neurons from death induced by a treatment with 24 h of hydrogen peroxide. Each flavone was applied 24 h prior to the oxidative insult, and neuronal viability was evaluated by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Results suggest that the ortho-dihydroxy substitution in the B-ring is not necessary to afford neuroprotection and could be partly responsible for neurotoxic effects. Furthermore, the hydroxy substitutions in the positions C3 (C-ring) in C5 and C7 (A-ring) would be important for neuroprotection in this model.

The neuroprotective capacity of individual flavonoids *in vivo* was confirmed also in a model of permanent focal ischemia (permanent Middle Cerebral Artery Occlusion - pMCAO). Administered in nanosomal preparations to facilitate the crossing of the blood brain barrier 30 min after vessel occlusion, quercetin, significantly decreased the brain ischemic lesion.

Our results *in vivo* and *in vitro* suggest that endogenous brain GSH is critical in the defence mechanisms after ischemia or oxidative insults and that quercetin increased the expression of the synthetic enzyme of GSH through NRf2 translocation to the nucleus.

We thus confirmed that flavonoids could protect the brain by their antioxidant capacity and also by their potential to modulate intracellular signals promoting cellular survival.

A group of quercetin-related flavonoids could be lead molecules for the development of neuroprotective compounds with multitarget anti-ischemic effects.