# α-synuclein antiaggregating properties and cytoprotective effects of curcumin and curcumin-derivatives

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A main goal in exploring therapeutic approaches for Parkinson's Disease (PD) is the design of small molecules that can simultaneously target aggregation of α-synuclein (AS) and oxidative stress. Recent experimental ?ndings indicate that various antioxidants, including polyphenols, have potent anti-?brillogenic effects and destabilize AS ?brils in in-vitro models. Speci?cally, the presence of 4-substituted-2-methoxy phenols seems to be an important structural and functional requirement for biological activity [1]. Within this class of compounds, curcumin, the principal curcuminoid present in the curry spice turmeric, has recently been shown to interact with AS reducing its cytotoxicity in a PD cell model [2]. Curcumin also possesses potent antioxidant and anti-in?ammatory properties and the ability to counteract numerous neurodegenerative processes such as apoptosis, mitochondrial dysfunction, microglial activation and protein aggregation. Unfortunately, curcumin has poor bioavailability due to its low solubility in aqueous solution and its rapid degradation at physiological pH into ferulic acid, vanillin and dehydrozingerone [3]. In this study, we examined the ability of dehydrozingerone its O-methyl derivative, zingerone, and their C-2 symmetric dimers (biphenyls) to interact with AS and to modulate its aggregation process, using biophysical techniques such as ?uorescence, circular dichroism (CD) and synchrotron radiation circular dichroism (SRCD). These results were compared with their antioxidant and neuroprotective activity. We found that the biphenyl zingerone analogue interacts with high af?nity with AS and also displays the best antioxidant properties while the biphenyl analogues are able to partially inhibit the aggregation process of AS. These results suggest
that a hydroxylated biphenyl scaffold may be used as a useful tool to develop compounds which are able to prevent the aggregation of AS and also possess antioxidant properties that may inhibit post translational modi?cations of AS caused by oxidative stress. It is well known that reactive oxygen/nitrogen species (ROS/RNS) react with susceptible amino acid residues of AS, inducing methionine oxidation, tyrosine nitration and dimer formation that were shown to promote the formation of oligomeric intermediates of AS [4, 5]. Moreover, preliminary results demonstrate that some of the studied molecules showed protective effects on PC12 cells exposed to hydrogen peroxide (0.075 mM), MPP+ (0.5 mM) or manganese chloride (0.75 mM).

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