The inhibition of α-synuclein aggregation using marine-derived bacterial metabolites as a novel neuroprotective approach for Parkinson's Disease

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Inclusions consisting of aggregated α-synuclein (α-syn), an abundant neuronal protein, are the most common histopathological finding in Parkinson's Disease (PD). The species thought to compromise the viability of neuronal cells are the soluble high molecular weight oligomers resulting from monomeric α-syn multimerization. The identification of therapeutic targets in PD is crucial, given the current lack of a definitive cure and the limited symptomatic relief provided by available medications. The marine environment, hosting a vast largely unexplored biodiversity, offers an enormous untapped resource for the discovery of novel biochemicals with diversified chemical structures containing new or uncommon functional groups thereby exhibiting more potent biological activities. In this work, we have screened a panel of marine-derived bacterial extracts to discover agents that can drive the removal of aberrant α-syn assemblies. Initially, the homogenates of marine-derived bacteria were selected by their ability to hinder the elongation of pre-formed fibril seeds *in vitro* using a specific thioflavin T fluorescence assay[1]. The most potent extracts were subsequently administered in a well-established SH-SY5Y cell system in which the inducible expression of α-syn results in oligomer formation and cell death. The effects of the marine extracts in the levels of aggregated α-syn were assessed by an aggregate-specific ELISA assay[2]. The secondary metabolites isolated from the most potent marine extracts were administered to SH-SY5Y cells to assess which compounds contain anti-aggregation activity in a cellular context. Our results demonstrated that the extract BIO904 and its component BIO904-09, a 2,5-diketopiperazine, exhibited a significant dose-dependent decrease in the levels of aggregated α-syn.

References:

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