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Title
**Modulation Of The Amyloidogenic Pathway By A Novel B-Secretase Inhibitor (F70hab16) From Malaysian Endophyte *Cytospora Rhizophorae*, In Murine Models For Alzheimer's DiseasE**

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Alzheimer's disease (AD) is the most common form of dementia. Until recently, AD is managed by relieving the cognitive symptoms without addressing one of the purportedly fundamental causes of the disease which is the formation of the amyloid plaques. The deposition and aggregation of β-amyloid are key events in the onset, progression and pathogenesis of AD. Thus one of the emerging strategies in treating AD is to inhibit the enzyme responsible for the formation of amyloid plaques, which is β-site amyloid cleaving enzyme (BACE-1). Endophytes are currently viewed as an outstanding source of bioactive natural products and may provide BACE-1 inhibitors as potential drug candidates for the treatment of AD. A novel bioactive compound, F70HAB16 was successfully isolated from a local endophytic strain and was found to inhibit the BACE-1 enzyme *in vitro* (IC50=13 μM). Oral treatment with 5 mg/kg of F70HAB16 for 14 days in scopolamine-induced memory deficit mice model was found to restore memory impairment caused by scopolamine in the radial arm maze and Morris water maze (MWM) tasks. The same treatment was found to improve spatial memory and learning in MWM tasks in a transgenic mice model of AD (B6.129TG) carrying the human APP-Swedish mutation (K670N/M671L). Analysis of the blood plasma and brain tissue of the transgenic mice revealed that the expression of amyloidogenic proteins decreased following treatment with the BACE- 1 inhibitor. Oxidative stress may play a significant but yet undefined role in the development of AD. It was found that the administration of 5 mg/kg of the F70HAB16 reduced the lipid peroxidation index and restored the antioxidant activities of catalase, superoxide dismutase, glutathione reductase and glutathione in the brain tissue of the scopolamine-induced mice model. The treatment with 5 mg/kg of F70HAB16 also redressed the level of nitric oxide in the scopolamine-induced mice. Hence F70HAB16 may prove to be beneficial in the treatment of AD by alleviating the oxidative stress associated with this disease. Furthermore, F70HAB16 also demonstrated neuroprotective properties on the cholinergic system of the scopolamine-induced mice. Finally, metabolomics study of the blood plasma revealed that F70HAB16 down-regulated sphingolipids such as dihydrosphingosine, phytosphingosine and C16-sphinganin. These metabolites were recently proposed as biomarkers for AD since they were found to be up-regulated in the blood plasma of AD patients.