

Basic research on brain aging, dementia, and Alzheimer's disease

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Aging is one of the most prominent causes of neurodegeneration. In 2010, about 13.2% of Thai population is older person over the age of 60; and this number is expected to reach 20.5% in 2022. As the life expectancy has increased, so too has the prevalence of cognitive deficits. Brain deterioration during aging is associated with elevated oxidative damages, apoptosis, and inflammatory responses. These alterations eventually lead to neuronal loss and dysfunction of neuronal plasticity. Those pathological features are significantly intertwined with the mechanisms of neuronal aging such as accumulated oxidative stress, suppression of autophagy, protein misfolding, shortened telomeres, changes of epigenetic regulation, and complex relationships between brain and organismal aging such as hormonal systems. Dementia is a progressive loss of cognitive function affecting thinking and social abilities which can interfere with daily functioning. It affects approximately 5%-8% of individuals over age 65, 15%-20% of individuals over age 75, and 25%-50% of individuals over age 85. Pathological characteristics in brains of dementia are extracellular senile plaques composed of amyloid β -peptide ($A\beta$) and intracellular neurofibrillary tangles consisting of hyperphosphorylated tau. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 50%-75% of the total, with a greater proportion in the higher age ranges. In addition, metal ions in the brain tissue of AD patients such as copper, iron, and zinc were also found to build up in the AD brain, upregulate the production of reactive oxygen species (ROS) and increase senile plaque formation as a result of the disease. Several studies based on cholinergic function in AD patients suggested a strong reduction of acetylcholine in the basal forebrain and hippocampus which are involved in cognitive performance. Risk factors for AD include age, family history, genetic factors (apolipoprotein E), traumatic brain injury, environment, obesity, and diabetes. There are currently no specific treatments that can impede the progression of AD. There are some factors that may reduce risks of AD including exercise, sufficient sleep, natural supplements, calorie restriction, mentally challenging leisure activities such as reading, playing games or playing a musical instrument and frequent social interactions. In our previous studies, we demonstrated that natural

compounds can prevent A β neurotoxicity via the reduction of ROS production, suppression of apoptosis, attenuation of inflammation, and prevention of cell death. Recently, stem cells have been actively investigated in several studies and they have shown some benefits to replace the neuronal loss in AD patients.

Keywords: Aging, dementia, Alzheimer's disease, natural compounds, antioxidant, apoptosis, anti-inflammation, stem cells

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Research Interests : Neurobiology of Alzheimer's disease

In our laboratory we study the mechanisms causing neuronal degeneration in Alzheimer's disease (AD) and the development of Thai medicinal plants for pharmaceutical therapy in AD. The initial approach involved the reduction of calcium-binding proteins in the AD brain. We have developed a system called a rapid and non-isotopic chain reaction-single strand conformation polymorphism (PCR-SSCP) method for determining the distribution of APOE genotypes in AD patients. This study confirmed that the APOE e4 allele is a risk factor in Thai AD patients, whereas the APOE e2 allele is commonly found in an age-matched subjects. In cell culture models, our findings show that β -amyloid induces neuronal death through the p75 neurotrophin receptor. In parallel, we have been investigating Thai medicinal plants for therapeutic use. As expected our findings show that N-trans feruloyltyramine, an antioxidant, purified from *Polyalthia suberosa* has protective effects against β -amyloid-induced neurotoxicity and oxidative stress in cortical cell cultures. In human neural stem cells (hNSC), current studies are investigating the mechanisms of the genetically modified hNSC secreting neurotrophins such as BDNF, GDNF, NT-3 and IGF-I. Those cells can protect neuronal death and enhance ChAT expression when they co-cultured with rat septal cells treated with β -amyloid.

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