## **Evaluation of Amyloid-β Aggregation and β-Secretase Inhibition Profile for Alzheimer's Disease Based on Biologically Active Natural Products**

Dementia is a broad category of brain diseases that cause deterioration in memory, thinking, behavior, and the abilities to perform everyday activities. According to the World Health Organization (2017), 50 million people worldwide have dementia, and this number will reach to 152 million in 2050. Dementia is caused by a variety of diseases and injuries, most importantly Alzheimer's disease (AD) making up 60% to 70% of cases.<sup>1</sup> AD is a primarily disease of old age, and it has become a serious problem with the general life-expectancy gradually increasing. A definitive diagnosis of AD requires the presence of severe dementia and also confirmation of two histopathological features, including extracellular amyloid plaques and intracellular neurofibrillary tangles, in the brain. Amyloid  $\beta$  (A $\beta$ ) peptide generated from amyloid- $\beta$  precursor protein (APP) through the actions of  $\beta$ - (BACE1) and  $\gamma$ -secretases is a principle component of the insoluble plaques. In A $\beta$ aggregation process, one monomer of  $A\beta$  interacts with other monomers to form dimers, oligomers, fibrils, and eventually insoluble deposits. Aß oligomers and fibrils are the most common forms found in brain of AD patients, and it is believed that these forms are more pathogenic than other intermediate aggregates.<sup>2,3</sup> Moreover, A gagregation has been shown to trigger inflammatory response, oxidative injury, and neurotoxicity resulting in dementia.<sup>4,5</sup> Therefore, the A $\beta$  inhibition is considered as a potentially valuable therapeutic approach for AD.

To date, there is no cure for AD; available drugs (donepezil, rivastigmine, galantamine, and memantine) can only delay worsening of symptoms. Therefore, developing effective treatments for AD is medical challenge of this century. AD pathogenesis is widely believed to be driven by A $\beta$  in the brain.<sup>2-5</sup> The significant attention has been paid to identify small-molecule natural products, such as polyphenolic derivatives (Fig. 1), that reduce A $\beta$  aggregation and A $\beta$  production.<sup>6,7</sup> Herein, inhibitors of A $\beta$  aggregation and BACE1 from natural products/ natural product-derived compounds, originated from plant and microbial sources, have been investigated using Thioflavin T (Th-T) assay, and through enzymatic (FRET) and cell-based assays, respectively.



Figure 1. Polyphenolic derivatives as inhibitors of Aβ aggregation and BACE1

<sup>&</sup>lt;sup>1</sup> World Health Organization. Dementia (2017) Retrieved from http://www.who.int/news-room/fact-sheets/detail/dementia.

<sup>&</sup>lt;sup>2</sup> Finder VH, Glockshuber R. Amyloid-β aggregation. *Neurodegener. Dis.*, **4**, 13-27 (2007).

<sup>&</sup>lt;sup>3</sup> Reitz C. Alzheimer's disease and the amyloid cascade hypothesis: a critical review. Int. J. Alzheimers. Dis., 2012, 369808 (2012).

Varadarajan S, Yatin S Aksenova M, Butterfield DA. Review: Alzheimer's amyloid beta-peptide-associated free radical oxidative stress and neurotoxicity. J. Struct. Biol., **130**, 184-208 (2000). <sup>5</sup> Irvine GB, El-Agnaf OM, Shankar GM, Walsh DM. Protein aggregation in the brain: The molecular basis for Alzheimer's

and Parkinson's diseases. Mol. Med., 14, 451-464 (2008).

<sup>&</sup>lt;sup>6</sup> Ono K, Hamaguchi T, Naiki H, Yamada M. Anti-amyloidogenic effects of antioxidants: Implications for the prevention and therapeutics of Alzheimer's disease. Biochim. Biophys. Acta., 1762, 575-586 (2006).

Ramassamy C. Emerging role of polyphenolic compounds in the treatment of neurodegenerative diseases: A review of their intracellular targets. Eur. J. Pharmacol., 545, 51-64 (2006).