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Polyphenols isolated from leaves of *Vitis thunbergii var.* taiwaniana regulate APP related pathway

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ABSTRACT

Alzheimer's disease (AD) is a neurodegenerative disorder characterized by the accumulation of amyloid plaques and neurofibrillary tangles in the brain. The major component of the plaques, amyloid-β (Aβ), is generated from amyloid-β precursor protein (APP) by β- and γ-secretase-mediated cleavages. Multiple lines of evidence demonstrate that overproduction/accumulation of Aβ in vulnerable brain regions is a primary cause of the pathogenesis of AD. Among the twelve polyphenols isolated from the leaf extracts of *Vitis thunbergii var.* taiwaniana (VTT), stenophyllol C, stenophyllol B, ampelopsin C, vitisin A, and davidiol A were shown to significantly reduce both Aβ40 and Aβ42 levels in N2a695 cells. Further studies revealed that ampelopsin C and vitisin A reduce Aβ production through inhibiting β-secretase activity, while the effects of the other active polyphenols on reducing Aβ generation are through different mechanisms. These results suggest that VTT extracts may be beneficial for AD prevention and treatment.

Alzheimer's disease (AD) is a devastating neurodegenerative disorder characterized by impaired memory and cognition. It is estimated that there are more than 30 million people worldwide afflicted with AD, and this figure is projected to grow to more than 106 million people by 2050.[1] AD has thus become a severe burden for both families and societies. AD has two major pathological hallmarks as senile plaques that are composed of heterogenous amyloid-β (Aβ) peptides and intra-neuronal fibrillary tangles that consist of hyperphosphorylated tau protein. Ample evidence indicates that Aβ peptides play a central role in AD pathogenesis.[2] Aβ peptides (e.g., $Aβ_{40}$ and $Aβ_{42}$, two major isoforms of Aβ) are proteolytic products of the amyloid-β precursor protein (APP) and are generated through sequential cleavages by enzymes called β- and γ-secretases (i.e., APP amyloidogenic processing). APP can also be cleaved by α-secretase within the Aβ domain and thus Aβ generation is precluded (i.e., APP non-amyloidogenic processing). The transmembrane aspartic protease β-site APP cleaving enzyme 1 (BACE1) has been identified as the essential β-secretase,[3–6] which is a major determinant that predisposes the brain to Aβ amyloidogenesis.[7,8] Multiple studies demonstrate that level and activity of BACE1 are increased in postmortem AD brains[9–11] suggesting a causative role in AD. Although homozygous BACE1 knock-out mice have retinal pathology,[12] partial hypomyelination at the developmental stage[13] and schizophrenia like behavior,[14] heterozygous mice are healthy and partial inhibition of BACE1 does not seem to cause any abnormal phenotypes. Notable, deficiency in BACE1 blocks Aβ production in the brain and ameliorates cognitive deficits in APP transgenic AD mice.[15–17] Therefore, inhibition of Aβ production, especially through inhibiting β-secretase (BACE1) activity, is considered as a promising strategy for the mechanism-based therapy for AD.

Vitis thunbergii var. taiwaniana (VTT) is a wild grape native to Taiwan where, along with other species of *Vitis* spp., has been used as a folk medicine or an edible plant.[18] The roots of *Vitis thunbergii* are traditionally used for the treatment of diarrhea, fracture and injury, jaundice, and hepatitis in Taiwan.[19] Its fruits are also used for making grape juice and wines by some aboriginal people of Taiwan.[20] The active components from VTT were reported to be resveratrol

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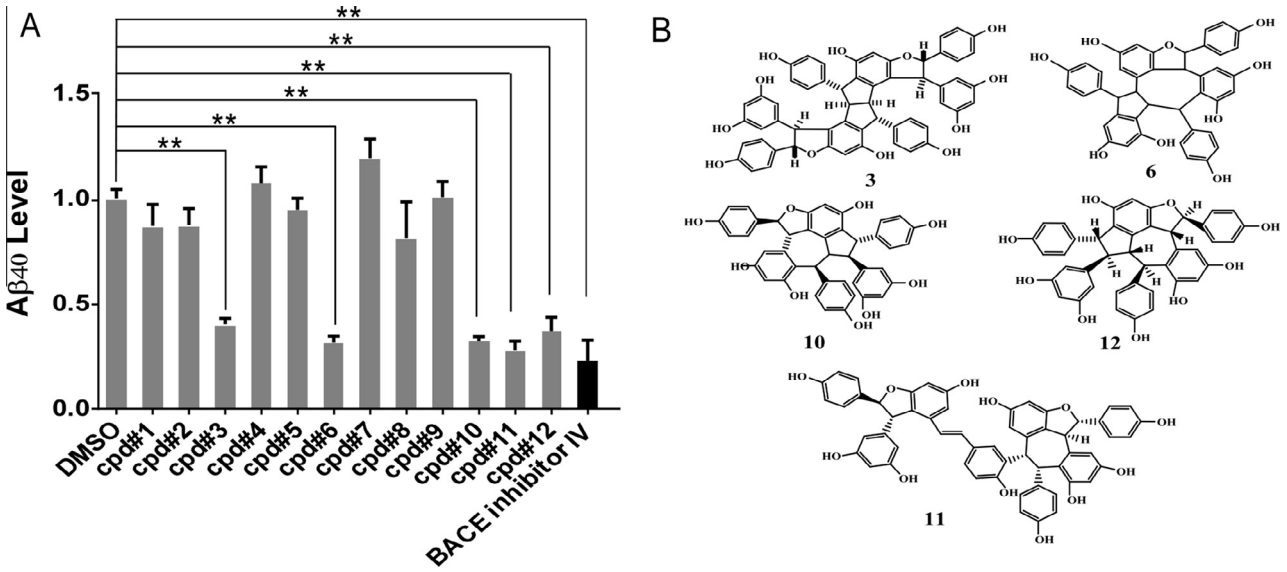

Figure 1. Compounds isolated from VTT inhibit Aβ secretion. (A) N2a695 cells were treated with compounds (10 μM) isolated from VTT and BACE1 inhibitor IV (10 μM, as a positive control) for 10 h. Aβ40 levels in conditioned media were measured by ELISA, and compared to those of DMSO treatment control (set as one arbitrary unit). Data represent mean ± SEM, $n = 3$, $^{**}p < 0.01$. (B) Structures of the five functional compounds.

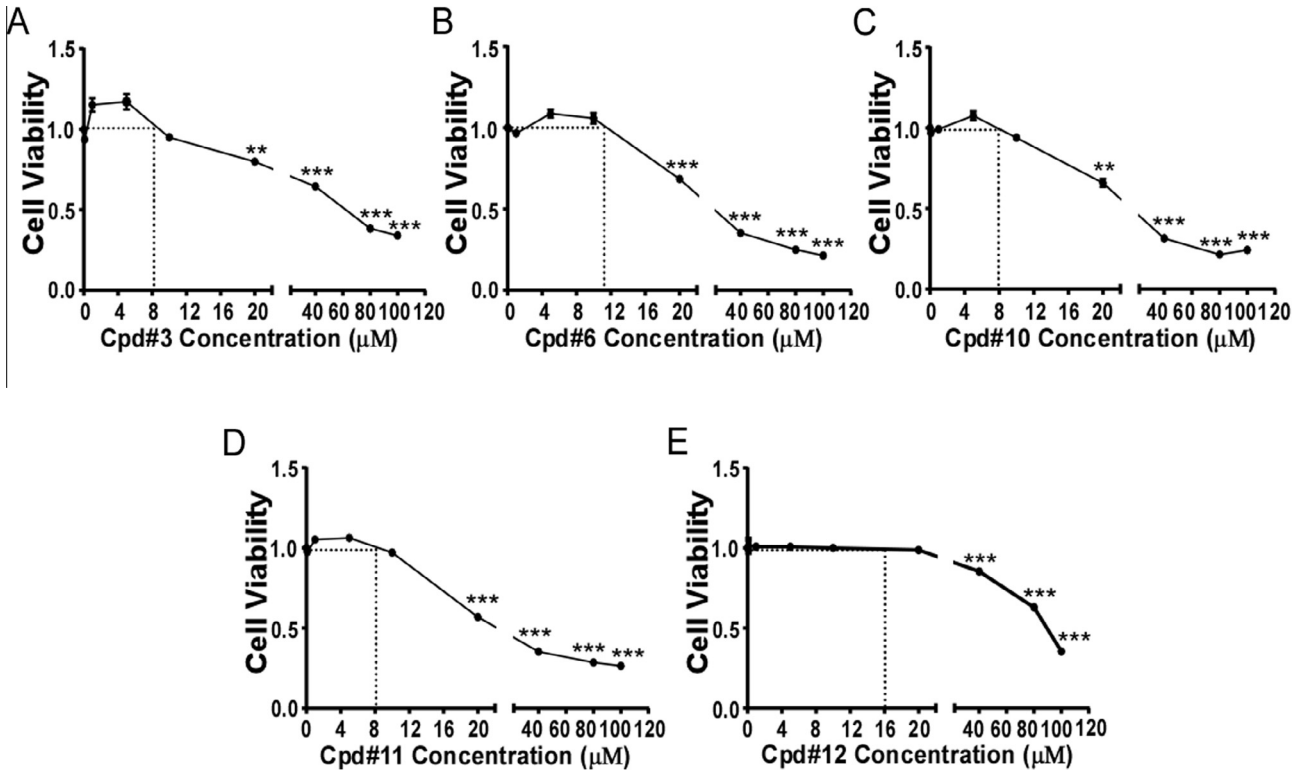

Figure 2. Cytotoxic effects of selected compounds. N2a695 cells were treated with compounds (A) **3**, (B) **6**, (C) **10**, (D) **11**, and (E) **12** at various concentrations (0, 0.1, 1, 5, 10, 20, 40, 80, and 100 μM) for 10 h. Cell viability was evaluated by CCK-8 assay, and compared to those of controls (set as one arbitrary unit). Data represent mean ± SEM, $n = 3$, $^{**}p < 0.05$, $^{***}p < 0.001$.

derivatives[21] and polyphenol compounds.[22] Recently, extracts or purified compounds from VTT were reported to have anti-microbial,[23] anti-inflammatory,[24] anti-hypertensive[25] and neuro-protective activities.[18] Among these natural products, stilbenes were major cause for the neuroprotective activities. Stilbenes from other herbs of *Vitis* sp. exhibited the same biological activity.[26–28]

Herein, we isolated twelve oligostilbenes from the leaf extracts of VTT and found that five of them could reduce Aβ level in cell culture studies. Among the five active compounds, two (**10** and **11**) were found to reduce Aβ production through inhibiting β-secretase activity and the other three compounds (**3**, **6** and **12**) decrease Aβ production likely through other mechanisms. The development of

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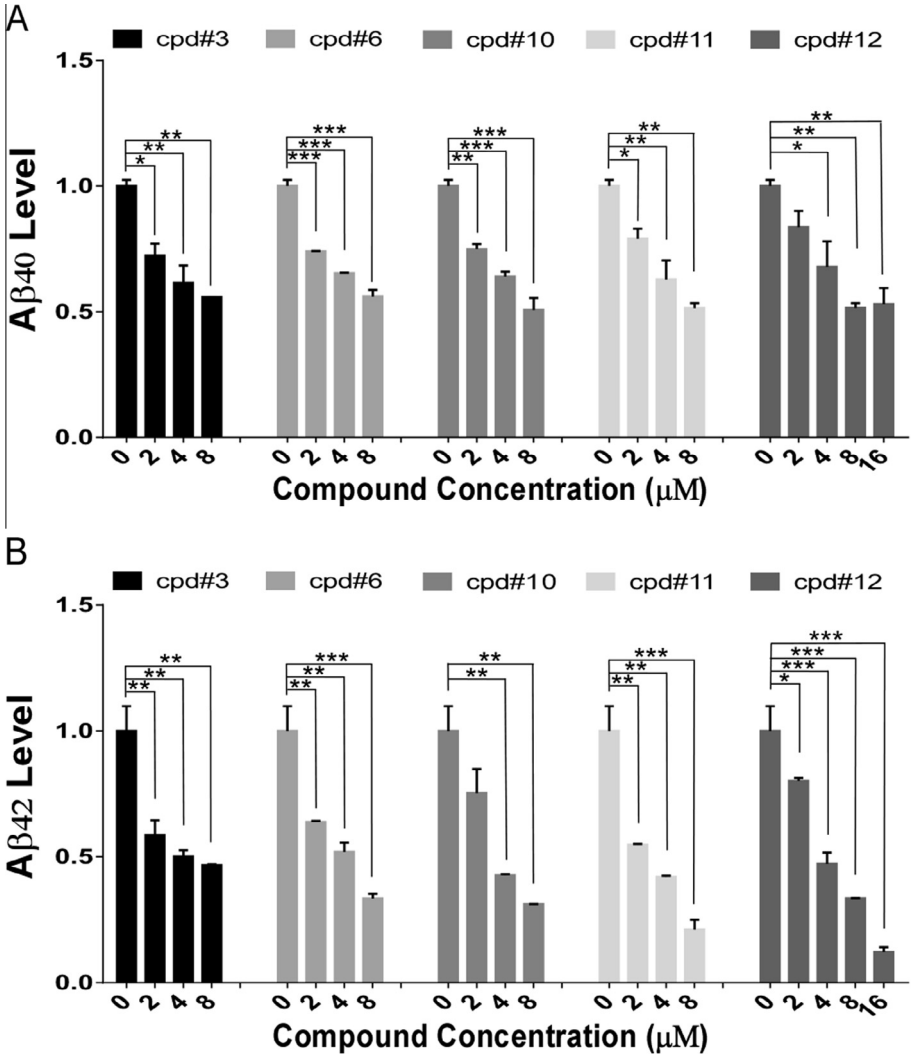

Figure 3. Selected compounds reduces Aβ40 and Aβ42 secretion. N2a695 cells were treated with 0–8 μM compounds **3**, **6**, **10**, and **11**, or 0–16 μM compound **12** for 10 h. (A) Aβ40 and (B) Aβ42 levels in conditioned media were measured by ELISA, and compared to those of controls (set as one arbitrary unit). Data represent mean ± SEM, $n = 3$, $^{*}p < 0.05$, $^{**}p < 0.05$, $^{***}p < 0.001$.

VTT extracts as functional foods or drugs may be beneficial for AD prevention and treatment.

Twelve compounds were isolated from the leaf extracts of 60% ethanol extract of *Vitis thunbergii var.* taiwaniana. Their structures were identified by the comparison with literature as polydatin (**1**),[29] *trans*-ε-viniferin (**2**),[24] stenophyllol C (**3**),[30] (+)-α-viniferin (**4**),[31] schizandriside (**5**),[32] stenophyllol B (**6**),[33] lyoniresinol 3α-*O*-β-D-glucopyranoside (**7**),[34,35] vitisin B (**8**),[24] urolignoside (**9**),[36] ampelopsin C (**10**),[24] vitisin A (**11**),[24] and davidiol A (**12**).[37]

In order to explore whether these twelve compounds could affect Aβ production, N2a695 cells were treated with these compounds (10 μM) and BACE1 inhibitor IV (10 μM, as a positive control) for 10 h. Aβ40 levels in conditioned media were then measured by ELISA. We found that the secretion of Aβ40 was significantly decreased by treatment with compounds **3**, **6**, **10**, **11**, and **12** (Fig. 1A). The five active compounds (structures seen in Fig. 1B) were then subject to further investigation.

To assess cytotoxicity of these compounds, N2a695 cells were treated with compounds **3**, **6**, **10**, **11**, and **12** at various concentrations (0, 0.1, 1, 5, 10, 20, 40, 80, and 100 μM). The effects of different compounds on cell viability were evaluated by CCK-8 assay. The results showed that cells remained viable when treated with 0–16 μM concentrations of compound **12** or 0–8 μM concentrations of compounds **3**, **6**, **10** and **11**. At higher concentrations, all these compounds caused a dose-dependent cytotoxic effect (Fig. 2).

We then treated N2a695 cells with 0–8 μM concentrations of compounds **3**, **6**, **10** and **11**, and 0–16 μM concentrations of compound **12** for 10 h. The results showed that all of these compounds dose-dependently reduced both Aβ40 and Aβ42 levels in conditioned media (Fig. 3).

Because γ-cleavage of APP is the final step for Aβ generation,[38] it is possible that these compounds may inhibit γ-secretase activity and thus reduce Aβ production. γ-Secretase is an internal protease that cleaves within the membrane-spanning domain of its substrate proteins, including APP and Notch. To determine whether these compounds could affect γ-secretase activity, we transfected N2aWT cells with NotchΔE (a truncated Notch molecule) and treated cells with these compounds. The generation of NICD was measured as an indicator of γ-secretase activity in the cells. We found little change of NICD in compound-treated cells compared to that in control cells (Fig. 4A and B), suggesting that γ-secretase activity was not affected. In addition, we found that compound treatment did not affect the protein level of the N terminal fragment (NTF) of PS1 that is an important γ-secretase component (Fig. 4A).

To investigate the mechanism underlying these compounds' inhibitory effect on Aβ generation, we treated N2a695 cells with

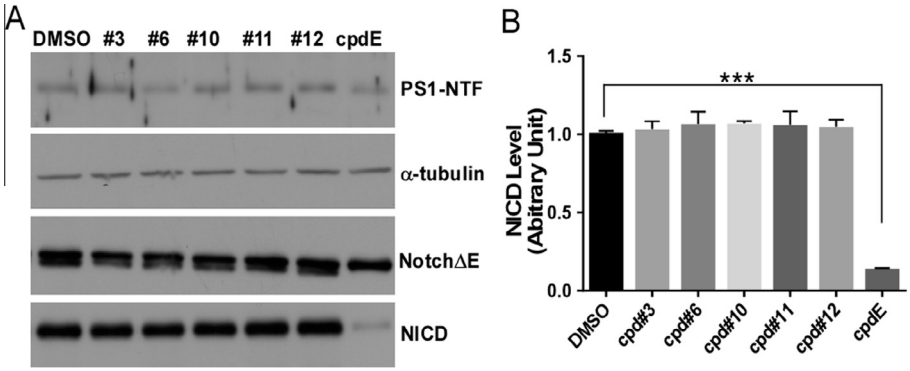

Figure 4. Selected compounds do not affect γ-secretase activity. (A) N2aWT cells were transfected with NotchΔE and then treated with 8 μM compounds **3**, **6**, **10**, **11**, and **12**, or with 0.5 μM compound **E** (cpdE) for 10 h. Equal protein amounts of cell lysates were analyzed by Western blot. (B) NICD levels were determined by densitometry, normalized to those of NotchΔE, and compared to that of DMSO treatment control (set as one arbitrary unit). Data represent mean ± SEM, $n = 3$, $^{***}p < 0.001$.

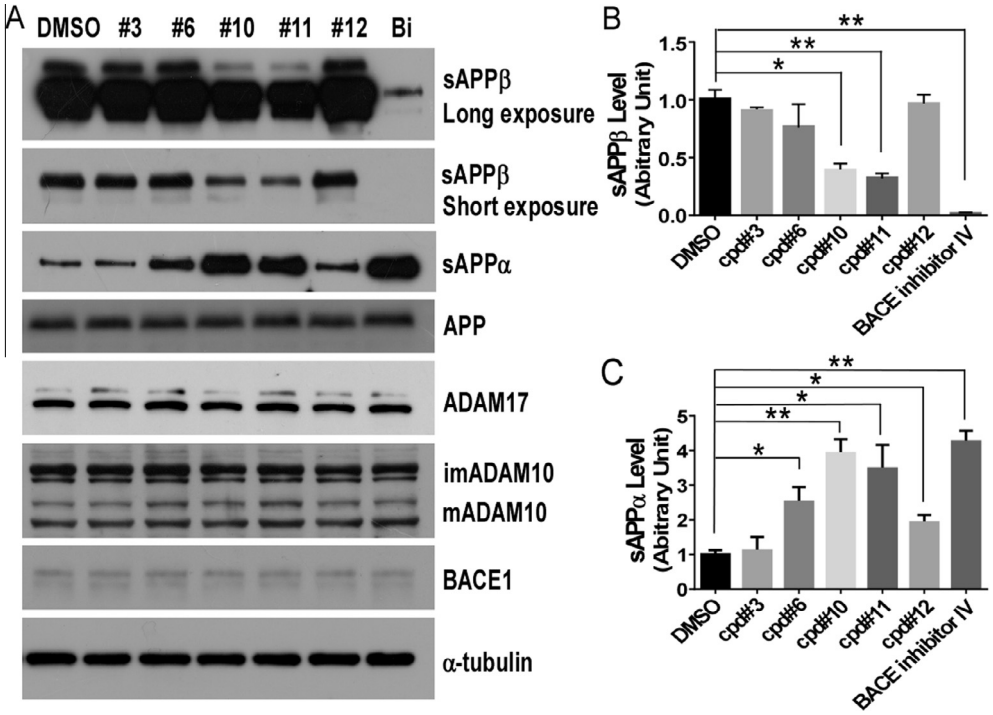

Figure 5. Effects of selected compounds on APP processing (A) N2a695 cells were treated with 8 μM compounds **3**, **6**, **10**, **11**, and **12**, or with 10 μM BACE1 inhibitor IV (Bi) for 10 h. Equal volume amounts of conditioned media were analyzed by Western blot for sAPPα and sAPPβ. Equal protein amounts of cell lysates were analyzed by Western blot for indicated proteins. (B) sAPPβ and (C) sAPPα levels were determined by densitometry, normalized to those of APP, and compared to those of DMSO treatment controls (set as one arbitrary unit). Data represent mean ± SEM, $n = 3$, $^{*}p < 0.05$, $^{**}p < 0.05$, $^{***}p < 0.001$.

these compounds (8 μM) for 10 h and detected the protein levels of APP and some of its metabolites (sAPPα and sAPPβ), BACE1, and two major α-secretase (ADAM10 and ADAM17/TACE). The results revealed that treatment with compounds **10** and **11** markedly decreased sAPPβ levels and increased sAPPα levels in a pattern similar to that found in samples treated with BACE1 inhibitor IV (Fig. 5A–C). Treatment with compounds **6** and **12** increased sAPPα levels and had no effect on sAPPβ generation. Treatment with compound **3** exhibited no impact on sAPPα or sAPPβ generation (Fig. 5A–C). In addition, none of these compounds affected the protein levels of full-length APP, BACE1, ADAM10 (both immature and mature forms), and ADAM17/TACE (Fig. 5A).

Moreover, we investigated whether these compounds may directly regulate β-secretase and/or α-secretase activities. We measured the β-secretase activity in mouse neuroblastoma N2a wild type cells (N2aWT) after treated with these compounds (8 μM) by using a commercial β-secretase activity kit. The results revealed that compounds **10** and **11** significantly inhibited β-secretase activity in N2aWT cells. We also examined the effects of these compounds on β-secretase activity in SH-SY5Y cells, a human neuroblastoma cell line. In accordance with the results seen in N2aWT cells, compounds **10** and **11** significantly inhibited β-secretase activity in SH-SY5Y cells. Compound **6** only significantly reduced β-secretase activity in SH-SY5Y cells but not in N2aWT cells. Compounds **3** and **12** exhibited little β-secretase inhibitory activity in both cells (Fig. 6A and B). Several enzymes have been identified that exhibit α-secretase activity and the metalloproteases ADAM17/TACE and ADAM10 are recognized as two major α-secretases.[39,40] Herein, we also detected the human TACE activity in SH-SY5Y cells after treated with these compounds (8 μM). We found that compounds

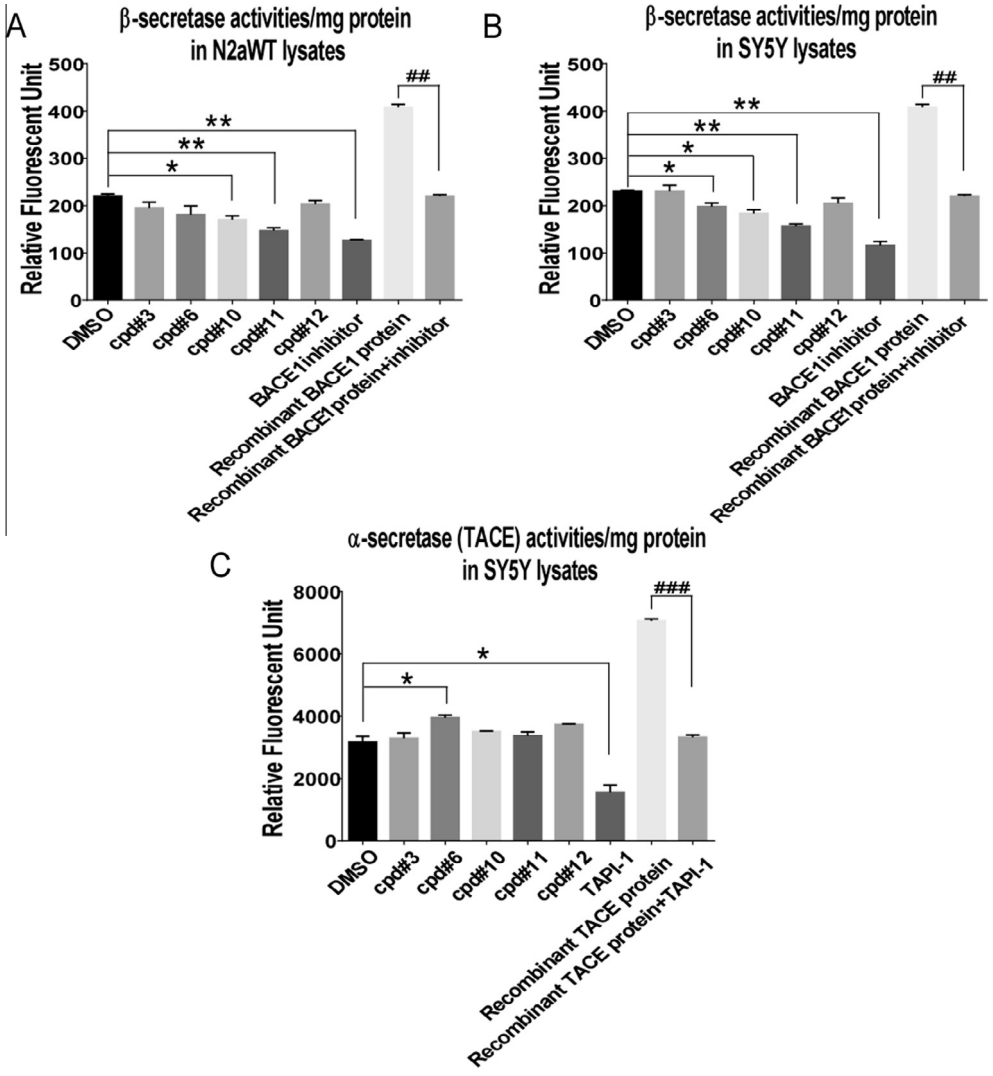

Figure 6. Effects of selected compounds on β-secretase and α-secretase activity. (A) N2aWT and (B) SH-SY5Y cells were treated with 8 μM compounds **3**, **6**, **10**, **11**, and **12** for 10 h. β-Secretase activity in cell lysates was assayed using a commercial kit. BACE1 inhibitor and recombinant BACE1 protein were used individually or collectively as different controls. (C) SH-SY5Y cells were treated with various compounds. TACE activity in cell lysates was assayed using a commercial kit. TAPI-1 and recombinant TACE protein were used individually or collectively as different controls. Data represent mean ± SEM, $n = 3$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{\#\#}p < 0.01$, $^{\#\#\#}p < 0.001$.

6 significantly increased TACE activity, whereas the other compounds had marginal effect on TACE activity (Fig. 6C). Together, these results suggest that compounds **10** and **11** reduce APP amyloidogenic processing through inhibiting β-secretase activity; compounds **6** reduces Aβ generation possibly through enhancing α-secretase activity and thus APP non-amyloidogenic processing; and the effects of compound **3** and **12** on Aβ reduction may be through a different mechanism that has yet to be clarified.

Natural products, particularly polyphenols, usually have good safety profiles and are widely used in alleviating common clinical disorders, including AD.[41,42] Polyphenols are abundant in diet, Fruits, vegetables, beverages (tea, wine and juice), plants, and some herbs are loaded with polyphenols. Several food-derived polyphenols, such as nobiletin,[43] luteolin,[44] and garcinol[45] have been demonstrated to be neuroprotective in vitro. Epigallocatechin-3-gallate (EGCG),[46] curcumin,[47] myricetin[48] and miyabenol C[49] have been shown to effectively reduce Aβ protein level and Aβ deposition in brain through various mechanisms, such as modulation of α-, β- and γ-secretases activities, inhibition of Aβ oligomer formation and inhibition of Aβ-induced neurotoxicity.

In this study, we isolated twelve polyphenols (Fig. 1B) from the leaf extracts of VTT and found that five of them can dramatically reduce Aβ secretion (Figs. 1A and 3) in cell culture. Among these five compounds, compounds **10** and **11** do not affect γ-secretase and α-secretase. In contrast, although compounds **10** and **11** treatments do not affect protein level of the essential β-secretase BACE1, they reduce cell-based β-secretase activity (Figs. 4–6A and B), indicating that compounds **10** and **11** reduce Aβ generation through inhibiting β-secretase activity. Compound **6** does not affect γ-secretase while increasing the α-secretase activity significantly (Figs. 4 and 6C), suggesting that compound **6** reduces Aβ generation probably by elevating α-secretase activity. In addition, compounds **3** and **12** reduce Aβ secretion but do not affect γ-secretase, β-secretase and α-secretase; and the underlying molecular mechanisms remain to be elucidated.

The bioavailability of polyphenols within human body is usually very low mostly due to poor pharmacokinetic properties characterizing polyphenols. In contrast to this point, some recent studies reported that not all polyphenols showed poor pharmacokinetic properties. For example, caffeic acid 3,4-dihydroxyphenethyl ester (CADPE) was detected in blood and the organs (liver, kidney, heart, spleen, and brain) one min after tail intravenous administration, indicating that it could quickly distribute to these organs. Furthermore, CADPE was hydrolyzed both in mice and in vitro mouse plasma quickly, but was much stable in vitro human

plasma, indicating a better bioavailability in human than in mice.[50] An another example is ellagic acid (EA). EA pharmacokinetics showed high interindividual variability. EA bioavailability was limited by the pH, ellagitannin and protein environment. Increase the intake of free EA does not enhance its bioavailability but promotes urolithin production. As the unchanged fractions detected from the systemic circulation, the bioavailability of EA is not as low as previously thought.[51]

Even thought some polyphenols do show poor pharmacokinetic properties, we can use many strategies to improve the bioavailability of polyphenols. One strategy is to setup the chemical bond between polyphenol and phospholipid and the new molecule (called phytosome) showed much better absorption and bioavailability.[52–55] Another strategy used to improve the bioavailability depends upon increasing the plasma half-life of the compound. For example, metabolic stability and clearance of peptides can be improved by cyclization,[56,57] halogenation,[58] methylation[59,60] and cationization.[61,62] Bioavailability can also be improved by vector-mediated transport, involving conjugation of the nutraceutical to a targeting molecule/substance, which has affinity for its receptors on the target tissue.[63]

Taken together, our results indicate that VTT provides a useful resource for screening BACE1 inhibitors and other Aβ-lowering compounds. Extracts and compounds isolated from VTT may be used to develop functional foods or drugs for inhibiting Aβ production and preventing/treating AD.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2015.11.085.

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