Tropical Journal of Pharmaceutical Research November 2017; 16 (11): 2629-2635
**ISSN:** 1596-5996 (print); 1596-9827 (electronic)


Available online at http://www.tjpr.org
**http://dx.doi.org/10.4314/tjpr.v16i11.9**

**Original Research Article**

# Effect of natural antioxidants on the aggregation and disaggregation of beta-amyloid

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*Sent for review: 9 July 2017* *Revised accepted: 16 October 2017*

## *Abstract*

***Purpose:*** *To examine the relationship between higher antioxidant activity and aggregation or disaggregation of beta-amyloid (Aβ) for 21 plants.*
***Methods:*** *Twenty-nine natural plant extracts and their antioxidant activities were analyzed using DPPH assay. The aggregation and disaggregation of Aβ were analyzed using Thioflavin-T assay.*
***Results:*** *Eleven plant extracts exhibited high antioxidant activities with the half-maximal inhibitory concentration ($IC_{50}$) values < 20.0 μg/mL. Furthermore, the plant extracts efficiently inhibited Aβ aggregation with a mean $IC_{50}$ value of 17.0 μg/mL. However, four plant extracts exhibiting low antioxidant activities ($IC_{50}$ > 80.0 μg/mL) inhibited Aβ aggregation less efficiently with a mean $IC_{50}$ value of 75.7 μg/mL. Furthermore, plant extracts with high antioxidant activities were not invariably efficient for disaggregating pre-formed Aβ aggregates.*
***Conclusion:*** *High antioxidant activities were positively correlated with the inhibition of Aβ aggregation, although not with the disaggregation of pre-formed Aβ aggregates. Nevertheless, potent antioxidants may be helpful in treating Alzheimer's disease.*

***Keywords:*** *Alzheimer's disease, β-Amyloid, Aggregation, Disaggregation, Antioxidants*

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## INTRODUCTION

β-amyloid (Aβ) is a polypeptide of 36-43 amino acids, and is a major causative factor of Alzheimer's disease (AD). Aβ aggregation into senile plaques is a pathological characteristic detected in the brains of patients with AD. Aβ is produced by the sequential cleavage of amyloid precursor proteins by β- and γ-secretases. Aβ molecules undergo self-aggregation to form oligomers and fibrils, which cause neurotoxicity via oxidative stress, disturb calcium homeostasis, and induce mitochondrial dysfunction, and neuro-inflammation. Thus, the discovery of compounds or extracts that inhibit Aβ aggregation, and induce the disaggregation of Aβ aggregates could be an effective approach to the therapy and prevention of AD.

Antioxidants are molecules that scavenge free radicals and reactive oxygen species (ROS), which can induce oxidative stress, and consequently, cellular damages. Antioxidant intake is helpful in preventing human diseases [1]. For example, antioxidants can reduce the risk of cardiovascular diseases by inhibiting vascular inflammation, lipid peroxidation, and platelet aggregation [2]. Additionally, antioxidants are known to have anti-cancer, anti-diabetic, and anti-aging effects [3-5]. Antioxidants are also considered helpful in treating AD, because the ROS generated in AD pathology causes neuronal damage [6]. Furthermore, certain

antioxidants such as polyphenols inhibit Aβ aggregation, and destabilize preformed Aβ aggregates [7,8]. However, the relationships between antioxidant activity and inhibition of Aβ aggregation, and between antioxidant activity and disaggregation of preformed Aβ aggregates are not analyzed. Therefore, in this study, 29 natural plant extracts with diverse antioxidant activity were analyzed for effects on the aggregation and disaggregation of Aβ, and the correlation between them was analyzed as well.

## EXPERIMENTAL

### Materials and reagents

Thioflavin T (ThT), DPPH, and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich (MO, USA). Ethanol and methanol were purchased from Samchun (Pyeong-Taek, Korea). $A\beta_{1-42}$ was purchased from GL Biochem (Shanghai, China).

### Plant materials

Twenty-nine plant materials (Table 1) were purchased from a commercial market (Samhing medicinal herb market; Seoul, Korea) in 2014. One of the authors (S-Y Park) performed botanical identification and voucher specimens were deposited in Pharmacognosy laboratory of College of Pharmacy, Dankook University.

### Preparation of plant extracts

Dried and pulverized plant materials were extracted 3 times with 90 % methanol at room temperature. The MeOH filtrate was evaporated under vacuum to yield the MeOH extract. Each extract was dissolved in DMSO and stored at -20 °C until use for the assay.

### Antioxidant assay

The antioxidant activities of the plant extracts were determined using a stable free radical, DPPH. The ability of the plant extracts to scavenge DPPH, and convert it to 1,1-diphenyl-2-picrylhydrazine was determined colorimetrically. In brief, the plant extracts at different concentrations of (4, 20, and 100 µg/mL) were mixed with 190 µL of DPPH (0.316 mM in ethanol) and the mixtures were incubated at 37 °C for 30 min. The optical density values of the mixtures were measured at 517 nm with a microplate reader (Molecular Devices, Sunnyvale, CA, USA). All measurements were conducted out at least thrice.

### ThT assay of inhibition of Aβ aggregation

To quantify Aβ aggregates, the ThT assay was performed. $A\beta_{1-42}$ was dissolved in DMSO at 1 mL, and stored at -20 °C until use. To monitor their effects on Aβ aggregation, the plant extracts (4, 20, and 100 µg/mL) were incubated with 20 µM of Aβ (49 µL) at 37 °C for 24 h. Then, 3 µM of ThT (50 µL) was added, and the fluorescence was measured after 30 min with an EMax precision microplate reader (Molecular Devices) with excitation at 442 nm and emission at 485 nm. Aβ treated with DMSO was used as the control, and each assay was performed in triplicate.

### ThT assay of disaggregation of preformed Aβ aggregates

To monitor the effects of the plant extracts on the disaggregation of the Aβ aggregates, 20 µM of Aβ (49 µL) was incubated at 37 °C. After 24 h, the plant extracts (4, 20, and 100 µg/mL) were added, and incubated for an additional 24 h. Subsequently, 3 µM of ThT (50 µL) was added, and the fluorescence was measured as described in the previous section.

### Statistical analysis

Data were expressed as means ± SD. Two or more group comparisons were performed by one-way analysis of variance (ANOVA), followed by Tukey's post-hoc test (SPSS version 17.0; IBM SPSS, Armonk, NY, USA). Differences were considered statistically significant at $P < 0.05$.

## RESULTS

### Antioxidant effects of the plant extracts

The results of DPPH assay showed that *Agrimonia pilosa*, *Cornus officinalis*, *Rubus coreanus*, *Sophora japonica*, and *Paeonia suffruticosa* exhibited strong antioxidant effects with $IC_{50}$ values below than 10 µg/mL. Contrastingly, *Houttuynia cordata*, *Torilis japonica*, *Rehmannia glutinosa*, and *Arisaema erubescens* exhibited relatively poor antioxidant activities with $IC_{50}$ values higher than 100 µg/mL (Table 1).

### Inhibition of Aβ aggregation by the plant extracts

The ThT assay demonstrated that *Cornus officinalis* exhibited the highest inhibitory effect on Aβ aggregation with an $IC_{50}$ value of 8.2 µg/mL (Table 1).

**Table 1:** List of some plant species, and their antioxidant, anti-amyloidogenic and Aβ disaggregating activities

| Plant | Plant part used | Antioxidant effect ($IC_{50}$, µg/mL) | Inhibition of Aβ aggregation ($IC_{50}$, µg/mL) | Disaggregation of Aβ aggregates ($ED_{50}$, µg/mL) |
|---|---|---|---|---|
| *Agrimonia pilosa* Ledebour (Rosaceae) | Whole plant | 5.1 | 9.1 | 102.3 |
| *Amomum villosum* Loureiro (Zingiberaceae) | Fruit/Seed | 17 | 13.8 | 39.9 |
| *Arisaema erubescens* Schott (Araceae) | Root | 90.9 | 98.3 | 114.2 |
| *Chelidonium majus* Linné var. asiaticum Ohwi (Papaveraceae) | Aerial parts | 78.2 | 72.4 | 104.2 |
| *Chrysanthemum zawadskii* Herbich var. latilobum (Maxim.) Kitamura (Compositae) | Whole plant | 27.8 | 46.4 | 179.7 |
| *Cimicifuga heracleifolia* Komarov (Ranunculaceae) | Rhizome | 52.7 | 76.1 | 115.7 |
| *Cornus officinalis* Siebold et Zuccarini (Cornaceae) | Fruit | 5.3 | 8.2 | 42.1 |
| *Cyperus rotundus* L (Cyperaceae) | Rhizome | 26 | 15.2 | 42.9 |
| *Drynaria fortunei* J. Smith (Polypodiaceae) | Rhizome | 19.7 | 16.1 | 134.9 |
| *Epimedium koreanum* Nakai (Berberidaceae) | Aerial parts | 46.8 | 39.4 | 110.6 |
| *Eucommia ulmoides* Oliver (Eucommiaceae) | Leaves | 72.5 | 56.1 | 234.1 |
| *Houttuynia cordata* Thunberg (Saururaceae) | Aerial parts | 134.4 | 99.3 | 276.4 |
| *Hovenia dulcis* Thunb (Rhamnaceae) | Fruit/Seed | 31.4 | 46.6 | 124.6 |
| *Leonurus japonicus* Houttuyn (Labiatae) | Aerial parts | 64.1 | 47.9 | 25.7 |
| *Magnolia obovata* Thunberg (Magnoliaceae) | Bark | 30 | 49.3 | 130.3 |
| *Morus alba* Linne (Moraceae) | Leaves | 74.2 | 44.5 | 73.8 |
| *Myristica fragrans* Houttuyu (Myristicaceae) | Seed | 59 | 51.3 | 88.4 |
| *Paeonia lactiflora* Pall (Ranuculaceae) | Root | 10 | 24.4 | 48.2 |
| *Paeonia suffruticosa* Andrews (Paeoniaceae) | Root bark | 7.8 | 20.8 | 92.9 |
| *plantago asiatica* L (Plantaginacea) | Seed | 12.8 | 20.6 | 127.7 |
| *Prunella vulgaris* L (Labiatae) | Stem | 14.6 | 24.8 | 45 |
| *Rehmannia glutinosa* Liboschitz ex Steudel (Scrophulariaceae) | Root | 109.5 | 80.2 | 396.9 |
| *Rubus coreanus* Miquel (Rosaceae) | Fruit | 6 | 12.8 | 146.1 |
| *Schizonepeta tenuifolia* Briquet (Labiatae) | Flower | 29.8 | 32.1 | 57.7 |
| *Scrophularia buergeriana* Miquel (Scrophulariaceae) | Root | 53.8 | 72.8 | 67.4 |
| *Sophora japonica* L (Leguminosae) | Flower | 7.1 | 25.2 | 134.3 |
| *Thuja orientalis* L (Curpressaceae) | Leaves | 16.7 | 10.8 | 14.7 |
| *Torilis japonica* Decandolle (Umbelliferae) | Fruit | 100.9 | 87.5 | 377.6 |
| *Zingiber officinale* Roscoe (Zingiberaceae) | Rhizome | 65.7 | 47.2 | 137.4 |

Aβ incubation with 100 μg/mL *C. officinalis* reduced the extent of Aβ aggregation to 23 %, compared with the DMSO-treated control groups (Figure 1A). Similarly, *Thuja orientalis* and *Agrimonia pilosa* had strong inhibitory effects on Aβ aggregation with $IC_{50}$ values of 9.1 and 10.8 μg/mL (Table 1), respectively. *T. orientalis* and *A. pilosa* at 100 μg/mL reduced Aβ aggregation to 16.5 % and 26.2 %, respectively, compared with the DMSO-treated control groups (Figure 1A). However, *Torilis japonica*, *Arisaema erubescens,* and *Houttuynia cordata* were less efficient in inhibiting Aβ aggregation, and their $IC_{50}$ values were 87.5, 98.3 and 99.3, respectively (Table 1). Incubation with 100 μg/mL *T. japonica*, *A. erubescens,* and *H. cordata* reduced Aβ aggregation to 47.2 %, 49.9 %, and 43.6 %., whereas these plant extracts at 4 μg/mL exhibited negligible inhibitory effects on Aβ aggregation (Figure 1B).

**Effects of the plant extracts on disaggregation of Aβ aggregates**

The disaggregating effects of the 29 plant extracts on pre-aggregated Aβ aggregates were determined by the ThT assay. *Thuja orientalis* exhibited the highest disaggregating activity among the 29 plant extracts with an $IC_{50}$ value of 14.7 μg/mL (Table 1). Similarly, *Leonurus japonicus* efficiently induced the disaggregation of preformed Aβ aggregates with an $IC_{50}$ value of 25.7 μg/mL. Contrarily, the effects of *Torilis japonica* and *Rehmannia glutinosa* on the disaggregation of preformed Aβ aggregates were extremely minimal with $IC_{50}$ values of 377.6 and 396.9 μg/mL, respectively.

**Antioxidant activity and inhibition of Aβ aggregation**

To determine the relationship between the inhibition of Aβ aggregation and antioxidant activity, twenty-nine plants were divided into 4 groups based on the $IC_{50}$ values for antioxidant activity (group 1, $IC_{50}$ value: 0–20; group 2, $IC_{50}$ value: 21–50; group 3, $IC_{50}$ value: 51-80, and group 4, $IC_{50}$ value over 81). The average $IC_{50}$ values for the antioxidant activities of the groups 1, 2, 3, and 4 were 11.1, 32.0, 65.0, and 86.1 μg/mL, respectively (Figure 2A), whereas the average $IC_{50}$ values for anti- Aβ aggregation in the groups 1, 2, 3, and 4 were 17.0, 38.2, 58.5 and 75.7 μg/mL, respectively. The average $IC_{50}$ value for anti- Aβ aggregating activities of the plant extracts in group 1 was significantly lower than those of the groups 2, 3, and 4. These results indicated that the plant extracts with higher antioxidant activities exhibited higher anti-Aβ aggregating activities. Therefore, plants with higher antioxidant activities could be beneficial for patients with AD because of their possibly higher anti-Aβ aggregating activities.

**Antioxidant activity and disaggregation of Aβ aggregates**

To determine the relationship between antioxidant activity and the disaggregation of Aβ aggregates, the mean $IC_{50}$ values of groups 1-4 for the disaggregation of Aβ aggregates were compared (Figure 2C). The average $IC_{50}$ values of the groups 1, 2, 3, and 4 for Aβ disaggregation were 84.3, 107.6, 105.8, and 291.2 μg/mL, respectively. Group 1 exhibited a relatively low $IC_{50}$ value for Aβ disaggregation; however, it was not significantly different from those of groups 2 and 3. However, the disaggregating activities of groups 1, 2, and 3 were significantly different from that of group 4.

## DISCUSSION

Natural products containing polyphenolic compounds, such as berries, spices, and green tea, are known to have antioxidant and neuroprotective activities. Furthermore, the neuroprotective effects of natural polyphenolic compounds, such as myricetin and luteolin are exerted, at least partially, by attenuating Aβ-induced toxicity [9].

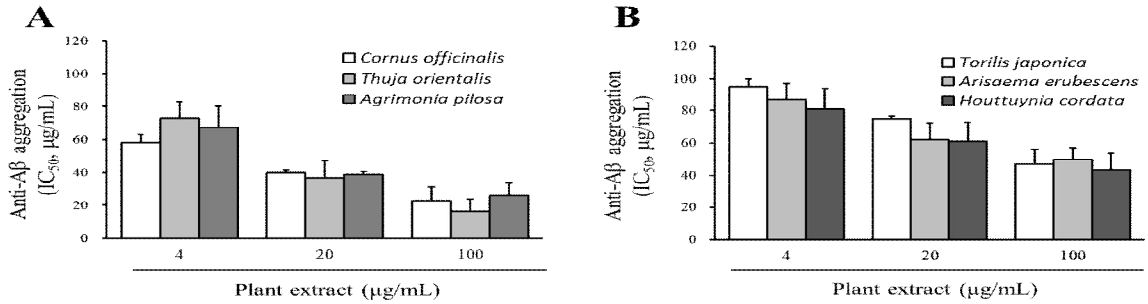


**Figure 1:** Anti-amyloidogenic effects of the plant extracts. (A) Anti- Aβ aggregation effects of the plant extracts, such as *Cornus officinalis*, *Thuja orientalis* and *Agrimonia pilosa,* with high antioxidant activity ($IC_{50}$ < 16.7 μg/mL). (B) Anti-Aβ aggregation effects of the plant extracts, such as *Torilis japonica*, *Arisaema erubescens*, and *Houttuynia cordata,* with low antioxidant activity ($IC_{50}$ > 90 μg/mL).

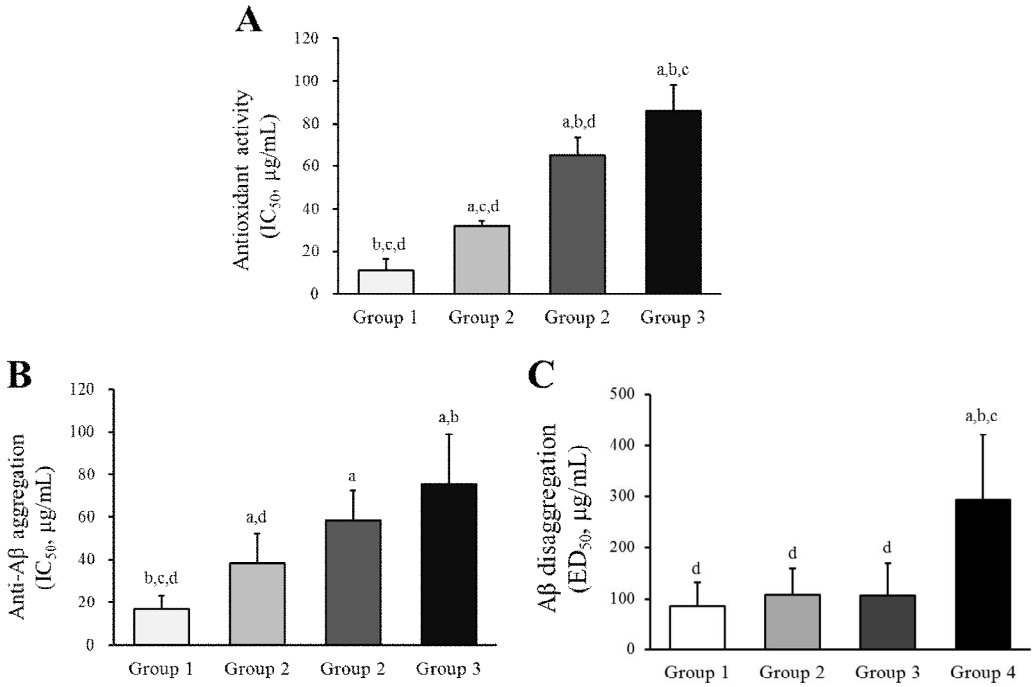


**Figure 2:** Mean values of the antioxidant, anti-Aβ aggregating and Aβ-disaggregating activities of 29 plant extracts divided into 4 groups based on antioxidant activity. (A) Average values of antioxidant activities, (B) average values of anti- Aβ aggregating activities and (C) average values of Aβ-disaggregating activities. [a] $P < 0.05$, different from Group 1, [b] $P < 0.05$, different from Group 2, [c] $P < 0.05$, different from Group 3, [d] $P < 0.05$, different from Group 4

However, this does not indicate that potent antioxidants are efficient in the inhibition of Aβ aggregation and disaggregation of Aβ aggregates. Therefore, in this study, the relationships between antioxidant activity and inhibition of Aβ aggregation, and between antioxidant activity and disaggregation of preformed Aβ aggregates were examined.

The aggregation of Aβ monomers to form oligomers and fibrils (aggregates) induces neurotoxicity. Oxidative stress, induced during Aβ aggregation, disrupts synapses, and impairs the functions of synapses and membranes [10,11]. Thus, antioxidants could be helpful in treating AD by reducing oxidative stress-related neuronal damage. Additionally, the use of compounds or extracts inhibiting Aβ aggregation is considered a good approach to the therapy and prevention of AD. For example, flavonoids such as myricetin, quercetin, and kaempferol inhibited Aβ aggregation (exhibited anti-amyloidogenic activities) [12-14]. Additionally, rosmarinic acid and curcumin are other compounds that inhibit Aβ aggregation efficiently [15,16]. Interestingly, these compounds are known to have high antioxidant activities. Consistent with previous reports, our results suggested that the plant extracts with relatively high antioxidant activity inhibited Aβ aggregation efficiently. This could be because potent antioxidants, such as polyphenols, in the plant extracts interact with aromatic regions in Aβ, disrupt the self-assembly of Aβ into β-sheet conformational stacking, and eventually, inhibit Aβ aggregation [17].

Antioxidants are also considered efficient in disaggregating Aβ. Curcumin and β-carotene exhibited high Aβ-disaggregating activities owing to their symmetric rod-like structures and hydrophobic moieties that wedged into Aβ cores, and disrupt the β-sheet structures [18,19]. However, the increases in hydrophilicity reduced Aβ-disaggregating activity [18]. Furthermore, morin is an efficient Aβ-disaggregating flavonoid. The aromatic moiety and hydrogen-bonding capacity of morin are suggested to cause the disaggregation of Aβ aggregates [20]. These reports suggest that molecules with hydrophobicity, aromatic moiety, and hydrogen bonding-capacity might, at least, partially contribute to the disaggregation of Aβ aggregates. Consistent with these results, our study similarly suggested that antioxidants are not invariably positively correlated with high Aβ-disaggregating activity. Altogether, these results suggested that the plant extracts with high antioxidant activities are efficient in inhibiting Aβ aggregation; however, they were not invariably efficient in disaggregating Aβ aggregates. Nonetheless, antioxidants could be beneficial for patients with AD owing to their possible anti-Aβ aggregating and Aβ-disaggregating activities.

## CONCLUSION

Twenty-nine plant extracts have been analyzed for antioxidant, anti-amyloidogenic, and Aβ disaggregating activities. The plant extracts with high antioxidant activity inhibit Aβ aggregation more efficiently than those with low antioxidant activity; however, antioxidant activity correlates weakly with the disaggregation of pre-formed Aβ aggregates. Nevertheless, good antioxidants may be helpful in treating AD.

## DECLARATIONS

### *Acknowledgement*

This work was supported by Research Fund of Dankook University in the form of a grant to one of the authors (SY Park) in 2015.

### *Conflict of Interest*

No conflict of interest associated with this work.

### *Contribution of Authors*

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

### *Open Access*



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