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SHORT REPORTS

Neuroprotective effects of vomifoliol, isolated from *Tarenna obtusifolia* Merr. (Rubiaceae), against amyloid-*beta*$_{1-42}$-treated neuroblastoma SH-SY5Y cells

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Abstract
Phytochemical investigation on the leaves of *Tarenna obtusifolia* Merr. (Rubiaceae) led to the isolation and identification of vomifoliol (**1**), *p*-coumaric acid (**2**), and stigmasterol (**3**) based on spectroscopic analyses and comparison with the literature data. Compound **1** moderately inhibited the aggregation of amyloid-*beta* ($A\beta_{1-42}$) using the ThT assay (55.71% at 50 µM) and exhibited neuroprotective effects against amyloid-*beta* ($A\beta_{1-42}$)-induced cytotoxicity in neuroblastoma SH-SY5Y cells at 20 µM concentration. This is the first phytochemical study on *T. obtusifolia* and the first report on the Aβ aggregation activity and neuroprotective potential of vomifoliol (**1**).

Keywords Amyloid-*beta* · Neuroprotective effects · Rubiaceae · *Tarenna* · Vomifoliol

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder among the elderlies, which is characterized by memory loss, dementia, and steady deterioration of cognition (Bagyinzky et al. 2017). An estimate of 47 million elderlies worldwide are suffering from AD, and the figure may balloon to 131 million in 2050 (Emmerzaal et al. 2015). The pathogenesis of AD involves a complicated and an interconnected network of genetic and biochemical factors which have not been fully elucidated yet. The abnormal amyloid-*beta* deposition, tau protein aggregation, low levels of acetylcholine, oxidative stress, and neuroinflammation are some of the pathological characteristics associated with AD (Xia et al. 2019). There is no cure for AD yet, but strategic treatments in its early stage of detection prove to be beneficial.

Extensive studies on natural products are leading the way of extensive studies aimed at disclosing potential anti-AD drugs. These small molecules incorporates high structural chemical diversity. A good number of research focusing on natural products as therapeutic agents for AD have demonstrated that these small molecules favors neuroprotection against Aβ cytotoxicity and aggregation (Espargaro et al. 2017). Hence, the identification of plants as a possible source of pharmacologically relevant compounds against AD is warranted.

Members of the genus *Tarenna* Gaertn. (Rubiaceae) are shrubs or trees occurring from low to high elevation and distributed in tropical and subtropical regions, including Africa, Asia, and the Pacific islands (Naiki et al. 2017). There are about 200 species of *Tarenna* worldwide (Bridson and Robbrecht 1985; De Block et al. 2001). Among these, 19 out of 24 existing species in the Philippines are endemic (Pelser et al. 2011). Among the *Tarenna* species, *T. asiatica* is an economically important plant used in traditional folk medicine for a variety of conditions, including boils, external ulcers, sores, and wounds (Ramabharathi et al. 2014). Several studies on various *Tarenna* species have described their medicinal properties, such as antimicrobial (Jayasinghe et al. 2002; Karthikkumaran et al. 2014; Ramabharathi et al. 2014), antioxidant (Ramabharathi et al. 2014; Yang et al. 2007, 2009), anti-inflammatory (Amutha et al. 2012), and toxicity (Oloro et al. 2016) effects. Phytochemical

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investigation on the *Tarenna* species revealed the presence of triterpenoids and triterpenoid glycosides (Harinantenaina et al. 2019; Zhao et al. 2008, 2011, 2013), alkaloid (Takayama et al. 1992), iridoids and iridoid glycosides (Takeda et al. 1976; Yang et al. 2006), lignans (Yang et al. 2007, 2009), and sesquiterpenes (Salmoun et al. 2007). In our continuing search for bioactive compounds from the Rubiaceae plants, we herein report the first phytochemical study and biological activity on the *Tarenna obtusifolia* Merr. Because our research interests likewise include potential AD prevention natural products, we also report the neuronal protective SH-SY5Y cells and anti-amyloidogenic activities of vomifoliol (**1**).

Materials and methods

General experimental procedures

NMR spectra were recorded on a JEOL ECZR 600 spectrometer. Silica gel 7734 (Merck, Germany) or silica gel 9385 (Merck, Germany) was used for column chromatography (CC). Thin-layer chromatography (TLC) was performed on aluminum-backed plates coated with Si gel F254; plates were visualized by spraying with vanillin sulfuric acid and warming. Distilled technical grade CH_2Cl_2 was used for extraction of the plant material, while analytical grade solvents were used for column chromatography.

Plant material

Fresh leaves of *Tarenna obtusifolia* were collected in the seashore of Virgin Island, Cebu, Philippines (11° 21′ 66.00″ N, 123° 79′ 0.23″ E), in April 2017. This species is a shrub characterized by having glabrous styles and noticeable small flowers. It was identified and authenticated by Dr. Grecebio Jonathan Alejandro, a Philippine Rubiaceae specialist. A voucher specimen (USTH-17-007) was deposited at the University of Santo Tomas (UST) Herbarium.

Extraction and isolation of constituents

The air-dried, ground leaves (1.1 kg) were extracted exhaustively with CH_2Cl_2 (7.5 L) for three consecutive days and filtered. The combined filtrates were concentrated under reduced pressure to obtain the CH_2Cl_2 crude extract (83 g). The crude extract was subjected to silica gel CC using gradient hexane-CH_2Cl_2 and gradient CH_2Cl_2-MeOH to obtain four fractions DA–DD. Fraction DC was chromatographed on silica gel using gradient $CHCl_3$-MeOH to afford subfractions DC1–DC5. Subfraction DC3 was passed through silica gel (gradient hexane–EtOAc/EtOAc–MeOH) to obtain DC3A–DC3D. Subfraction DC3A was chromatographed using gradient $CHCl_3$-EtOAc to afford vomifoliol (**1**, 2.8 mg, white solid). Subfraction DC3B afforded stigmasterol (**3**, 28 mg, white solid) after silica gel chromatography (7:3 $CHCl_3$-EtOAc). Subfraction DC3C was purified on silica gel (gradient hexane–EtOAc) to afford *p*-coumaric acid (**2**, 0.9 mg, yellow solid). The isolated compounds (Fig. 1) were subjected to spectral analysis.

Vomifoliol (**1**): ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.25 (1H, d, J = 16.8 Hz, H-2a); 2.45 (1H, d, J = 16.8 Hz, H-2b); 5.91 (1H, br s, H-4); 5.78 (1H, d, J = 15.7 Hz, H-7); 5.87 (1H, dd, J = 15.7 Hz, 5.1 Hz, H-8); 4.42 (1H, m, H-9); 1.31 (3H, d, J = 6.3 Hz, H_3-10); 1.01 (3H, s, H_3-11); 1.09 (3H, s, H_3-12); 1.90 (3H, d, 1.5 Hz, H_3-13). ^{13}C NMR (150 MHz, $CDCl_3$): δ 41.1 (C-1); 49.7 (C-2); 197.9 (C-3); 127.0 (C-4); 162.6 (C-5); 79.0 (C-6); 135.7 (C-7); 129.0 (C-8); 68.1 (C-9); 23.8 (C-10); 22.9 (C-11); 24.0 (C-12); 18.9 (C-13).

p-Coumaric acid (**2**): ^{1}H NMR (600 MHz, CD_3OD): δ 7.56 (1H, d, J = 15.9 Hz, H-7), 7.44 (2H, d, J = 8.6 Hz, H-2, H-6), 6.79 (2H, d, J = 8.6 Hz, H-3, H-5), 6.28 (1H, d, J = 15.9 Hz, H-8).

Stigmasterol (**3**): ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.08 (1H, m, H-1a); 1.83 (1H, m, H-1b); 1.49 (1H, m, H-2a); 1.82

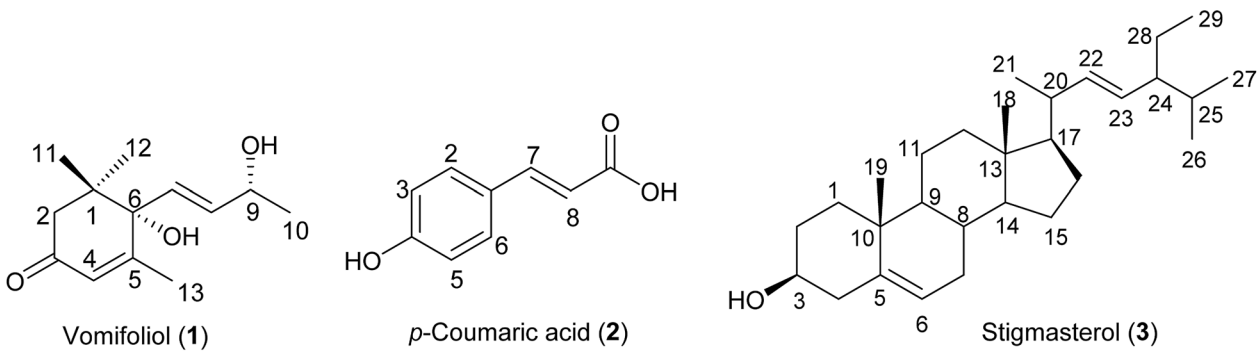

Fig. 1 Structures of compounds isolated from *Tarenna obtusifolia*

(1H, m, H-2b); 3.53 (1H, m, H-3); 2.26 (2H, m, H_2-4); 5.35 (1H, d, J = 4.7 Hz, H-6); 1.52 (1H, m, H-7a); 1.98 (1H, m, H-7b); 1.46 (1H, m, H-8); 0.94 (1H, m, H-9); 1.47 (2H, m, H_2-11); 1.15 (1H, m, H-12a); 1.97 (1H, m, H-12b); 1.00 (1H, m, H-14); 1.06 (1H, m, H-15a); 1.55 (1H, m, H-15b); 1.27 (1H, m, H-16a); 1.71 (1H, m, H-16b); 1.13 (1H, m, H-17); 0.70 (3H, s, H_3-18); 1.01 (3H, s, H_3-19); 2.04 (1H, m, H-20); 1.02 (3H, d, J = 6.8 Hz, H_3-21); 5.15 (1H, dd, *J* = 15.1 Hz, 8.4 Hz, H-22); 5.02 (1H, dd, *J* = 15.1 Hz, 8.4 Hz, H-23); 1.53 (1H, m, H-24); 1.44 (1H, m, H-25); 0.84 (3H, d, *J* = 6.4 Hz, H_3-26); 0.83 (3H, d, *J* = 6.3 Hz, H_3-27); 1.15 (1H, m, H-28); 0.80 (3H, t, *J* = 6.0 Hz, H_3-29).

Cytotoxicity assay

Neuroblastoma cells (SH-SY5Y), purchased from the American Type Culture Collection, were maintained in DMEM supplemented with 10% FBS, 1% kanamycin, and 1% penicillin. Cell cultures were maintained at 37 °C in 5% CO_2 and passaged once per week. The SH-SY5Y cells were subcultured into a 96-well plate at 1×10^4 cells/well and incubated for 24 h. After incubation, the cells were treated with compound **1** and incubated for another 72 h. The media were removed, and the wells were washed with PBS. Fresh media (100 µL) were added and incubated for another 30 min. After incubation, CellTiter-Glo® luminescent reagent (100 µL; Promega, Madison, WI, USA) was added, and the luminescence was measured using a PerkinElmer Victor-3® multi-plate reader (PerkinElmer, Waltham, MA, USA). The values representing cell viability are expressed as means ± standard deviation (SD) of three trial experiments.

Thioflavin T (Tht) fluorescense assay

Amyloid-*beta*$_{1\text{-}42}$ (10 µM) in PBS (pH 7.4) was incubated with or without the compound **1** at 37 °C for 24 h. Twenty microliters of ThT solution (50 µM) in glycine–NaOH buffer (pH 9) was then added. The fluorescence signal was measured (excitation wavelength, 450 nm; emission wavelength, 510 nm) using a PerkinElmer Victor-3® multi-plate reader. The percentage of aggregation inhibition was calculated using the following equation: $[(1 - I_{Fi}/I_{Fc}) \times 100\%]$, where I_{Fi} and I_{Fc} are the fluorescence absorbance with and without the inhibitors, respectively, after subtracting the background fluorescence of the ThT solution.

Neuroprotective activity

Neuroblastoma SH-SY5Y cells (2×10^4 cells/well) were cultured in 96-well plate and incubated for 24 h. After incubation, the cells were pre-treated with compound **1** (20 µM, 10 µM, 1 µM) for 2 h. After 2 h, the cells were combined with 1 µM A$\beta_{1\text{–}42}$ and incubated for another 24 h at 37 °C and 5.0% CO_2. A negative control (DMEM + 10% FBS) was used to normalize the % cell viability. The toxicity of SH-SY5Y cells treated with the extracts only and the SH-SY5Y cells treated with A$\beta_{1\text{-}42}$ only was also performed. After incubation, the percentage cell viability was determined using the CellTiter-Glo® luminescent reagent.

Table 1 SH-SY5Y Cytotoxicity of *Tarenna obtusifolia* CH_2Cl_2 Extract

Concentration, µg/mL	Cell viability (%)[a]
50	34.91 ± 3.21*
10	53.77 ± 2.46*
5	73.59 ± 1.57*
1	84.05 ± 0.56
0	100 ± 3.44

*Significant difference with the control cells (0 µg/mL) at $p < 0.05$

[a]The values are expressed as mean ± SD of three trial experiments

Table 2 A$\beta_{1\text{-}42}$ aggregation using Thioflavin T assay

Sample	% Inhibition[a]
Tarenna obtusifolia CH_2Cl_2 extract (50 µg/mL)	63.42 ± 3.42*
Tarenna obtusifolia CH_2Cl_2 extract (5 µg/mL)	14.10 ± 1.67
1 (50 µM)	55.71 ± 0.97
1 (5 µM)	11.08 ± 1.23
Phenol Red[b] (50 µM)	69.85 ± 0.29

*Statistically comparable to the postive control ($p < 0.05$)

[a]The values are expressed as mean ± SD of three trial experiments

[b]The positive control

Statistical analysis

The results are expressed as the mean ± SD of at least three trial experiments. The statistical significance was analyzed by one-way ANOVA or Student's *t* test and $p < 0.05$ was considered statistically significant.

Results and discussion

In our screening of biologically active Rubiaceae plant extracts using the neuroblastoma SH-SY5Y cell cytotoxicity (Table 1) and Thioflavin-T assay (Table 2), the CH_2Cl_2 extracts of *T. obtusifolia* showed inhibition of amyloid-*beta* aggregation and toxicity to the neuroblastoma cells. At the highest concentration (50 µg/mL), the extract exhibited a 75% cell growth inhibition (~ 35% cell viability).

A significant difference in the cell viability (Table 1) was shown in the percentage cell viability of the extract at 5, 10, and 50 µg/mL concentrations when compared to the negative control ($p < 0.05$). The extract exhibited a moderate (63.42%) inhibition of amyloid-beta aggregation at 50 µg/mL (Table 2). This result is also comparable to the phenol red as positive control (Necula et al. 2007; Wu et al. 2006) at $p < 0.05$.

Fractionation of the crude CH_2Cl_2 extract of *T. obtusifolia* using various chromatographic techniques led to the isolation of three compounds **1–3**. Structures of the isolated compounds were established using spectroscopic analyses as well as comparison with the literature data. The compounds were identified as vomifoliol (**1**) (Mogana et al. 2014), *p*-coumaric acid (**2**) (Rho and Yoon 2017), and stigmasterol (**3**) (Pateh et al. 2008) (Fig. 1). Compound **2** was previously isolated from *T. madagascariensis* (Djoudi et al. 2007). To the best of our knowledge, this is the first isolation of compounds **1** and **3** from the genus *Tarenna*.

As part of our research interest of searching for potential anti-neurodegenerative agents from nature, we screened the isolated compounds in a thioflavin T assay. Results of the ThT assay of **1** are presented in Table 2. The ThT assay describes the capacity of a compound or plant extract to inhibit the aggregation of β-amyloid (Aβ), one of the pathological characteristics identified with AD. Compound **1** showed a moderate activity in the prevention of the aggregation of Aβ at 50 µM. Both *p*-coumaric acid (**2**) (10.51% at 50 µM) and stigmasterol (**3**) (13.74% at 50 µM) did not exhibit any potent activity. Interestingly, vomifoliol isolated from *Canarium patentinervium* of family Burseraceae also showed anticholinesterase activity with an IC_{50} 96.64 ± 0.09 µg/mL (Mogana et al. 2014). In another study, the anti-neuroinflammatory activity of three isomers of vomifoliol were determined by measuring the NO levels produced in LPS-activated microglial cell line BV-2 with IC_{50} values ranging from 39 to 76 µM (Kim et al. 2015).

Compound **1** also exhibited an IC_{50} of 39.6 µM against the neuroblastoma SH-SY5Y cells utilizing the ATP assay after 72 h of cell incubation. Previous studies have also reported the cytotoxicity of **1** on various human cancer cell lines, such as HL-60 (IC_{50} 55.6 µM ± 0.5), Hep G2 (IC_{50} 45.5 µM ± 2.0), and COLO 205 (IC_{50} 6.8 µM ± 0.5) (Bai et al. 2011).

The neuroprotective effects of **1** in the SH-SY5Y cells were evaluated using $A\beta_{1-42}$-induced cells (Fig. 2). A 20 µM, 10 µM, and 1 µM concentrations of **1** were used based on the initial SH-SY5Y toxicity screening. At these concentrations, **1** did not exhibit significant cytotoxicity in the SH-SY5Y cells when compared to the control

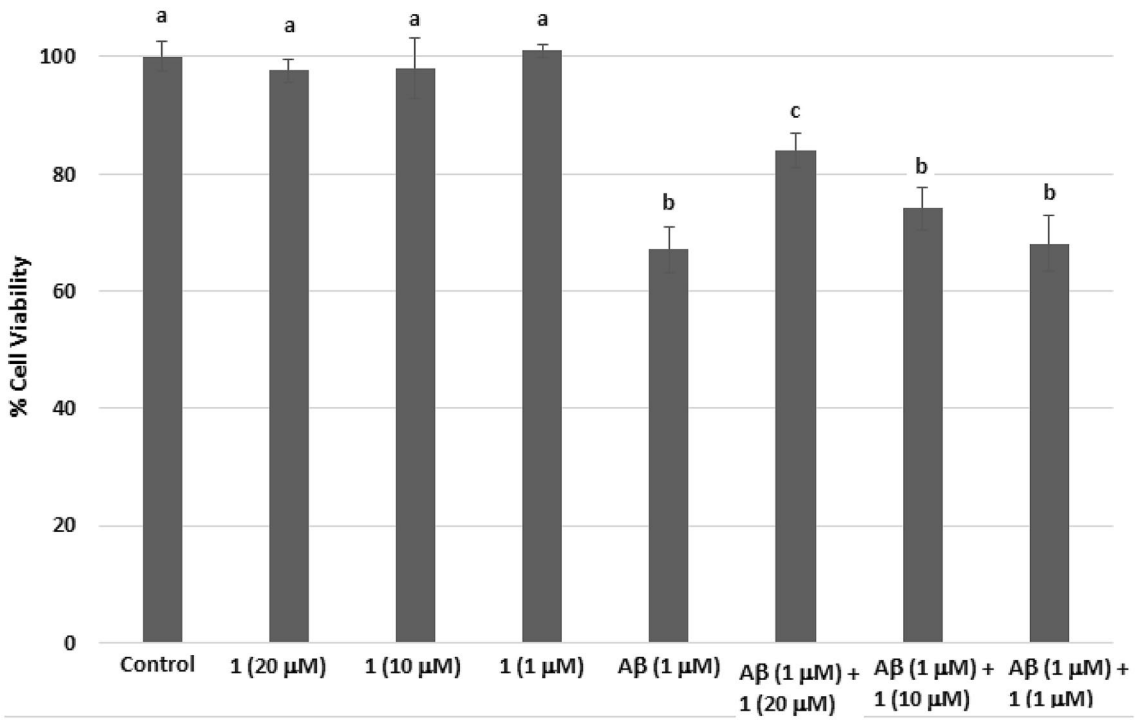

Fig. 2 Neuroprotective effects of vomifoliol (**1**) on amyloid-$beta_{1-42}$-induced neuroblastoma SH-SY5Y cells after 24 h of treatment. The results represent % cell viability vs control (no treatment) and indicate means ± SD of three trials. Significant difference at $p < 0.05$ is indicated by different lowercase letters. Only the 20 µM of **1** showed a significant neuroprotective effects on the amyloid-*beta*-damaged SH-SY5Y cells

($p < 0.05$) (Fig. 2). To assess the protective effects of **1** on SH-SY5Y damaged cells, the neuroblastoma cells were pre-treated with compound **1** for 2 h and incubated for 24 h with 1 µM $A\beta_{1-42}$ (Meng et al. 2018). Pre-treatment of the cells with **1** (20 µM) significantly protected ($p < 0.05$) the SH-SY5Y cells from the $A\beta_{1-42}$ when compared to the cells exposed only with the $A\beta_{1-42}$. In contrast, pre-treatment with 10 µM and 1 µM of **1** did not exhibit any protective effects to the cells when compared to the $A\beta_{1-42}$ only-treated cells ($p < 0.05$).

AD is often characterized by progressive loss of memory, mental ability, and language aptitude. Several key factors to combat the development and progression of AD is being undertaken, including the inhibition of Aβ deposition, oxidative stress reduction, and inhibition of tau protein aggregation. Plant extracts and their natural products have been given attention to disclose their capacity as anti-AD agents (Silva et al. 2014), focusing more into their ability to inhibit the Aβ aggregation (Espargaro et al. 2017). In this study, we have described the potential of vomifoliol (**1**), a norsesquiterpenoid, to inhibit the aggregation of Aβ. These type of small molecules, including iridoids and monoterpenoids, show diverse pharmacological activities which make them potential candidates as neuroprotective agents against AD (Habtemariam 2018).

Conclusion

This is the first phytochemical study on the aerial parts of *T. obtusifolia*. This is also the first report on the capability of vomifoliol (**1**) to inhibit the aggregation of $A\beta_{1-42}$ using the ThT assay and its neuroprotective potential in $A\beta_{1-42}$-treated SH-SY5Y cells at 20 µM concentration. Collective results on vomifoliol may suggest its promising potential as a possible candidate for neurodegenerative diseases warranting more chemical and pharmacological investigations including its mechanism of action.

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Author contributions MAT and SSAN conceptualized the study. MAT and SJBG performed the experiments. GJDA collected and identified the plant. MAT wrote the manuscript. GJDA and SSAN revised the manuscript. All authors read and approved the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

Ethics approval and consent to participate The article does not contain any studies involving human participants or animals.

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