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ACETYLCHOLINESTERASE INHIBITORY ACTIVITY OF THE METHANOL EXTRACT AND PHYTOCHEMICAL STUDY OF THE LEAVES OF *Macaranga gigantea* (Rchb.f. & Zoll.)

(Aktiviti Perencatan Asetilkolinesterase Terhadap Ekstrak Methanol dan Kajian Fitokimia ke atas Daun *Macaranga gigantea* (Rchb.f. & Zoll)

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Abstract

Genus *Macaranga* belongs to Euphorbiaceae family and is known for their mutualistic associations with ants. This plant is widely distributed in the tropics of Africa, South-East Asia, Australia and the South Pacific region. In folk medicine, traditional healers use fresh or dried leaves of *Macaranga* species to treat swellings, cuts, sores, boils and bruises. In this study, 20 µL methanol crude extract from the leaves of *Macaranga gigantea* was assayed for its *in-vitro* acetylcholinesterase inhibitory activity. The crude extract displayed a good acetylcholinesterase (AChE) inhibition activity at IC_{50} at 39.89 ± 4.57 ug/mL. Phytochemical study on the crude leaf extract lead to the isolation and purification of two pure compounds *via* radial chromatographic techniques. Based on the ^{1}H NMR and ^{13}C NMR analysis, the structure of the pure compounds was found to have a prenylated substituent which could be recognized through the presence of methyl, methylene, and a vinyl group. Based on the analysis of spectral data and comparison with literature, the compounds were elucidated as a geranylated stilbene, schweinfurthin C **(1)** and a farnesylated flavonol, macagigantin **(2)**.

Keywords: acetylcholinesterase, Euphorbiaceae, *Macaranga gigantea*, schweinfurthin C, macagigantin

Abstrak

Genus *Macaranga* tergolong di dalam famili Euphorbiaceae dan dikenali sebagai tumbuhan yang mempunyai hubungan mutual dengan semut. Tumbuhan ini boleh ditemui di kawasan tropika seperti Afrika, Selatan-Timur Asia, Australia dan di kawasan Selatan Pasifik. Menurut ilmu perubatan lama, pengamal perubatan mengunakan daun segar atau kering dari spesies *Macaranga* untuk mengubati bengkak, luka, sengal, lecur dan lebam. Melalui kajian ini, ekstrak mentah yang telah dilarutkan di dalam metanol telah diuji dengan aktiviti perencatan asetikolinesterase. Sebanyak 20 µL larutan ekstrak telah digunakan dan menunjukkan keputusan yang baik sebagai perencat asetilkolinesterase di IC_{50} 39.89 ± 4.57 ug/mL. Kajian fitokimia yang dijalankan telah

berjaya memisah dan menulenkan dua sebatian tulen menggunakan kromatografi radial. Bersandarkan pada data ^{1}H NMR and ^{13}C NMR, struktur sebatian tulen yang diperoleh mempunyai kumpulan prenil yang terdiri daripada metil, metilina dan vinil. Berdasarkan analisis data spektra ini dan perbandingan dengan literatur, sebatian-sebatian tulen tersebut dicirikan sebagai geranil stilbena, schweinfurthin C **(1)** dan farnesil flavonol, macagigantin **(2)**.

Kata kunci: asetilkolinesterase, Euphorbiaceae, *Macaranga gigantea*, schweinfurthin C, macagigantin

Introduction

Macaranga (known as Mahang) comes from the family of Euphorbiaceae which comprises 300 species [1, 2]. In Malaysia, this genus is commonly found in the village areas, wastelands, and swampy forests [3]. This genus is also widely distributed around the globe such as Africa, South-East Asia, Australia, South Pacific region, Burma, Indo China, China and India [4]. With a lot of sunlight in secondary forests, the plants can grow up to 20 m tall [5]. Species from this genus are well-known for their mutualistic association with the genus *Crematogaster* (Myrmicinae) ants [6]. *Macaranga* species is closely related to *Mallotus*, but several characteristics may differentiate the two such as the presence of red latex, the *Macaranga* myrmecophytic habit and the anatomy of the leaves [7]. The use of some *Macaranga* species in traditional medicine have led many researchers to carry out extensive studies on the bioactive compounds of the genus, thus validating the use of this genus as a therapeutic remedy. Numerous biological activities such as cytotoxicity, antioxidant, antiplasmodial, antimicrobial, anti-inflammatory and other types of activities have been reported from the extracts as well as individual compounds [8]. The leaves of *Macaranga gigantea* were selected as part of our current research on bioactive compounds in Malaysia. Two known compounds namely, schweinfurthin C **(1)**, a geranylated stilbene and macagigantin **(2)**, a farnesylated flavonol were isolated and purified. We herein report the isolation and elucidation of the compounds as well as assay of the crude methanol extract.

Materials and Methods

Instrumentation

The structure of the isolated compound was analyzed by 1D & 2D NMR. The ^{1}H NMR and ^{13}C NMR were analyzed in acetone-d_6 on Bruker 600 Ultrashield NMR spectroscopy measured at 600MHz and 150MHz respectively. The vacuum liquid chromatography technique (VLC) used Silica gel 60, 70-230 ASTM (MERCK 1.07747); aluminum supported silica gel 60 F254 was used for thin-layer chromatography (TLC) and the radial chromatography technique (RC) used the Si-gel 60 PF (Merck catalogue 254 number: 1.07749). The TLC plates were spotted using a fine glass capillary tube and were developed in a chromatographic chamber with various solvent systems at room temperature. The spots were then visualized under UV light (254 and 356 nm). The solvent used were *n*-hexane, chloroform, ethyl acetate, methanol, and acetone from RCI Labscan Limited, Thailand (AR grade solvent, 2.5L).

Plant material

A total of 7 kg *M. gigantea* leaves were collected from the forest area at Universiti Teknologi MARA, Puncak Alam. A voucher specimen (UKMB40430) consisting leaves, stems and fruit were submitted and deposited in UKM Herbarium.

Extraction and Isolation

Standard procedures for extraction and isolation of pure compounds from plant materials were applied in this research [9]. The 7 kg of *M. gigantea* leaves were rinsed carefully with tap water to remove dirt and were dried at room temperature for two weeks. The dried leaves were cut into small pieces and ground to powder using a grinder which resulted in 3 kg dried powder. The solvent used for extraction was methanol (AR grade solvent). The 3 kg of the sample were macerated in 30 liters of methanol for 72 hours at room temperature. The methanol extract was filtered using No 1 Whatman filter paper with a diameter circle of 25 mm. The extracts were then evaporated under reduced pressure at 20 mbar/ 50 °C using a rotary evaporator which resulted in the concentrated methanol extracts (270 g). The extracts were stored at 5 °C until further use. About 100 g of crude methanol extract was fractionated by using VLC

with solvent system *n*-hexane: ethyl acetate in 100 mL (100:0 to 50:50) four-time for each solvent system to give six (6) major fractions 1-6. Fraction 2 (1 g) was separated by RC eluted with chloroform: ethyl acetate (100 to 70:30) to afford compound **1,** schweinfurthin C (2 mg) and compound **2,** macagigantin (2 mg).

Acetylcholinesterase inhibitory activity assay

The spectroscopic method of Ellman et al. [10] was used as reference method as described by Salles et al. [11], in which thiocholine produced by the action of acetylcholinesterase forms a yellow color with 5, 5`-dithiobis(2-nitrobenzoic acid). Eserine was used as a positive control. A 96-well plate was designed by adding 190 µL DTNB solution, 20 µL samples and 20 µL enzyme solution, were mixed and incubated for 10 minutes at 37 °C. Then, 20 µL substrates were added to the wells. Measurement of the intensity of the product color was completed by reading the microplate reader kinetically at 412 nm, runtime 15 minutes and interval 1 minute, which is proportionate to the enzyme activity in the sample. The control contained all components except the tested sample. The percentage of AChE inhibitory activity (%IA) was calculated by using the following equation 1:

$$\%\text{IA} = \frac{\text{Negative control absorbance} - (\text{Sample absorbance} - \text{Blank absorbance})}{\text{Negative control absorbance}} \times 100 \quad (1)$$

Results and Discussion

The phytochemical screening (Table 1) on the crude methanol extract of *M. gigantea* showed the presence of flavonoid, tannin and terpene as illustrated by the red, green and reddish-brown solution form from Shinoda, tannin and terpenoid test respectively. This screening procedure was performed in triplicate and was repeated three times with similar results.

Spectral data of isolated compound

Compound **1**: A yellow solid. ^{1}H NMR (acetone-d_6, 600 MHz) spectral data: δ_H 6.93 (d,2.0, H-3), 6.81 (d, 2.0,H-5), 3.38 (t, 7.0,H-7), 5.37 (m,H-8), 1.75 (s,H-10), 1.98 (m,H-11), 2.11 (m, H-12), 5.14 (m, H-13), 1.59 (s, H-15), 1.74 (s, H-16), 6.83 (d, 16,H-1'), 6.74 (d, 16,H-2'), 6.58 (s, H-4'), 6.58 (s, H-8'), 3.35 (t, 7.2, H-"'), 5.34 (m, H-2"), 1.80 (s, H-4"). 1.94 (t, 7.4,H-5"), 1.98 (m, H-6"), 5.11 (m,H-7"), 1.59 (s, H-9"), 1.66 (s,H-10"). ^{13}C NMR (acetone-d_6, 150 MHz) spectral data: δ_C 143.0 (C-1), 144.6 (C-2), 110.2 (C-3), 131.4 (C-4), 119.8 (C-5), 130.6 (C-6), 28.1 (C-7), 122.9 (C-8), 136.4 (C-9), 15.3 (C-10), 39.6 (C-11), 29.4 (C-12), 124.2 (C-13), 133.6 (C-14), 16.8 (C-15), 24.9 (C-16), 129.7 (C-1'), 127.7 (C-2'), 137.2 (C-3'), 104.8 (C-4'), 156.1 (C-5'), 115.5 (C-6'), 156.1 (C-7'), 104.8 (C-8'), 22.1 (C-1"), 123.3 (C-2"), 134.5 (C-3"), 15.4 (C-4"), 39.7 (C-5"), 26.5 (C-6"), 124.3 (C-7"), 132.4 (C-8"), 17.0 (C-9"), 25.0 (C-10").

Compound **2**: A yellow solid. ^{1}H NMR (acetone-d_6, 600 MHz) spectral data: δ_H 6.62 (s, H-8), 8.15 (dd, 9.0, 2.4,H-2'/6'), 7.03 (dd, 7.0, 2.4, H-3'/5'), 3.40 (d, 7.2,H-1"), 5.32 (m, H-2"), 1.83 (s, H-4"), 1.98 (s, H-5"), 5.10 (m, H-6"), 1.77 (d, H-8"), 1.83 (s, H-9"), 5.04 (m, H-10"), 1.59 (s, H-12"), 1.54 (s, H-13"), 1.57 (s, H-14"), 1.60 (s, H-15"), 12.44 (s, 5-OH), 9.71 (br s, 7-OH), 7.98 (br s, 3-OH), 9.04 (br s,4'-OH).

Elucidation of compound 1 as schweinfurthin C

Compound **1** was obtained as a yellow solid. The ^{1}H NMR spectrum (Table 2) showed two *meta*-couple aromatic proton signals at δ_H 6.93 (H-3), δ_H 6.81 (H-5) and δ_H 6.58 (H-4'/8') indicating that the compound contained two aromatic rings with AB spin system. A stilbene skeletal was shown by two doublet signals at δ_H 6.83 (H-1') and δ_H 6.74 (H-2') representing the vinyl proton that connected the two phenolic rings. The substitution of two geranyl group in the structure was shown through the presence of six methyl singlets at δ_H 1.75 (H-10), 1.59 (H-15), 1.74 (H-16), 1.80 (H-4"), 1.59 (H-9"), 1.66 (H-10"), six methylene signals at δ_H 3.38 (H-7), 1.59 (H-15), 1.74 (H-16), 3.35 (H-1"), 1.94 (H-5"), 1.98 (H-6") and four vinyl signals at δ_H 5.37 (H-8),

5.14 (H-13), 5.34 (H-2"), 5.11 (H-7"). ^{1}H-^{13}C long-range HMBC correlation showed that H-1" correlated with C-5', C-6', C-7' and H-7 with C-1, C-5, C-6 which confirmed the attachment of geranyl substituent in the structure. Based on the analysis of spectroscopic data and comparison with the literature [12], compound **1** was assigned as schweinfurthin C (Figure 1).

Table 1. Phytochemical screening from crude methanol extract of *M. gigantea.*

Type of Compound	Crude Methanol Extract
Flavonoid	+++
Alkaloid	---
Saponin	---
Tannin	+++
Terpene	+++

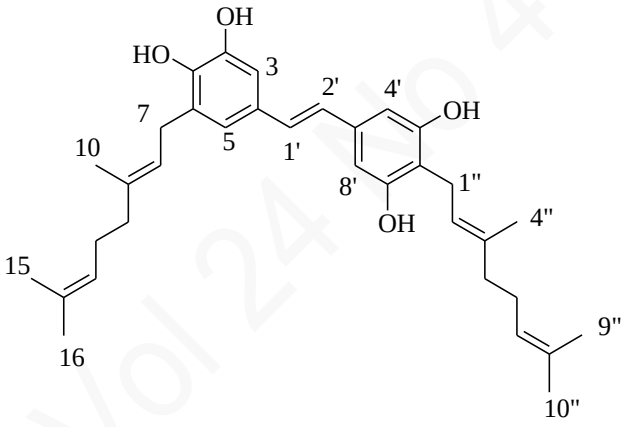

Figure 1. Structure of schweinfurthin C

Table 2. NMR Spectroscopy of Compound **1**

Position	δ_H (multi, *J* (Hz))		δ_C		^{1}H-^{13}C HMBC
	Compound 1	*Schweinfurthin C	Compound 1	*Schweinfurthin C	
1	-	-	143.0	144.2	-
2	-	-	144.6	146.1	-
3	6.93 (d, 2.0)	6.81 (d, 2.0)	110.2	111.0	C-1, C-5, C-2'
4	-	-	131.4	130.3	-
5	6.81 (d, 2.0)	6.67 (d, 2.0)	119.8	120.6	C-5, C-3, C-2', C-1
6	-	-	130.6	129.6	-
7	3.38 (t, 7.0)	3.34 (t, 7.0)	28.1	29.1	C-6, C-1, C-5
8	5.37 (m)	5.33 (t, 7.4)	122.9	124.1	C-8

Table 2 (cont'd). NMR Spectroscopy of Compound **1**

Position	δ_H (multi, *J* (Hz))		δ_C		^1H-^{13}C HMBC
	Compound 1	***Schweinfurthin C**	**Compound 1**	***Schweinfurthin C**	
9	-	-	136.4	136.6	-
10	1.75 (s)	1.72 (s)	15.3	16.2	-
11	1.98 (m)	2.04 (t, 7.8)	39.6	40.9	C-15, C-12, C-13, C-7, C-14
12	2.11 (m)	2.11 (t, 7.8)	29.4	27.7	C-12, C-11
13	5.14 (m)	5.14 (t, 7.2)	124.2	125.3	C-15
14	-	-	133.6	132.2	-
15	1.59 (s)	1.58 (s)	16.8	17.7	C-14
16	1.74 (s)	1.64 (s)	24.9	25.8	C-15, C-13
1'	6.83 (d, 16)	6.77 (d, 16)	129.7	129.0	C-3, C-5
2'	6.74 (d, 16)	6.63 (d, 16)	127.7	127.0	C-4'/8', C-2', C-1'
3'	-	-	137.2	137.7	
4'	6.58 (s)	6.43 (s)	104.8	105.7	C-4'/8', C-5', C-7'
5'	-	-	156.1	157.2	-
6'	-	-	115.5	115.8	-
7'	-	-	156.1	157.2	-
8'	6.58 (s)	6.43 (s)	104.8	105.7	C-4'/8', C-5', C-7'
1"	3.35 (t, 7.2)	3.27	22.1	23.2	C-6', C-5', C-7', C-2"
2"	5.34 (m)	5.24 (t, 7.4)	123.3	124.6	C-5"
3"	-	-	134.5	134.8	-
4"	1.80 (s)	1.75 (s)	15.4	16.3	C-5", C-7", C-3"
5"	1.94 (t, 7.4)	1.93 (t, 7.2)	39.7	41.0	-
6"	1.98 (m)	2.04 (t. 7.8)	26.5	27.8	C-5"
7"	5.11 (m)	5.07 (t, 7.0)	124.3	125.5	C-9"
8"	-	-	132.4	132.0	-
9"	1.59 (s)	1.56 (s)	17.0	17.8	C-10", C-5"
10"	1.66 (s)	1.62 (s)	25.0	25.9	-

Compound **1** NMR Spectra recorded at 600 MHz (^1H) and 150 MHz (^{13}C-APT) in acetone-d_6
Schweinfurthin C NMR Spectra recorded at 500 MHz (^1H) and 125 MHz (^{13}C-APT) in CD_3OD [12]

Elucidation of compound 2 as macagigantin

Compound **2** (Figure 2) was obtained as a yellow solid. The ^1H NMR spectrum displayed a chelated hydroxyl signal that appeared to be at the most deshielded at δ_H 12.44 (br s, 5-OH), δ_H 7.98 (s, 3-OH), δ_H 9.71 (s, 7-OH) and δ_H 9.04 (s, 4'-OH) showed that this compound is a flavonol from kaempferol derivative. Two proton signals, which is a pair of doublet for AA"BB" system at aromatic region δ_H 8.15 (dd, 9.0, 2.4, H-2'/6') and δ_H 7.03 (dd, 7.0, 2.4, H-3'/5') corresponds to the hydroxyphenyl group that attaches to C-4' at ring B. A singlet at δ_H 6.62 (H-8) in the aromatic region of ^1H NMR spectrum suggested there is a farnesyl group attached to ring A of flavonol group. This can be observed through the presence of four methyl's at δ_H 1.59 (s, H-12"), 1.54 (s, H-13"), 1.57 (s, H-14") and 1.60

(s, H-15"), five methylene at δ_H 3.40 (d, 7.2, H-1"), 1.83 (s, H-4"), 1.98 (s, H-5"), 1.77 (d, H-8") and 1.83 (s, H-9") and three methine vinyl protons at δ_H 5.32 (m, H-2"), 5.10 (m, H-6") and 5.04 (m, H-10"). Based on the ^{1}H NMR data (Table 3), compound **2** was confirmed as macagigantin. The spectral data were identical to that reported by Tanjung et al. [13].

The crude methanol extract was assayed for its *in-vitro* acetylcholinesterase inhibitory activity. Eserine was used as a positive control. The crude extract displayed a good acetylcholinesterase (AChE) inhibition activity at IC_{50} 39.89 ± 4.57 ug/mL. It is believed that the abundance of secondary metabolite compounds were responsible for this activity. A study by Howes & Perry stated that several flavonoids and stilbenoids inhibited AChE [14]. The catechol moiety on ring B of flavonoid compound formed a binding interaction with the active site of AChE enzyme which is the main cause factor of the activity [15].

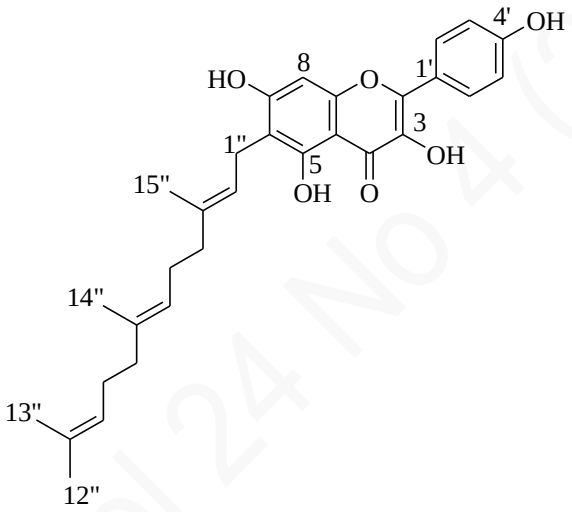

Figure 2. Structure of macagigantin **(2)**

Table 3. NMR Spectroscopic Data of Compound **2**

Position	**Compound 2** δ_H **(multi, *J* (Hz))**	**Macagigantin*** δ_H **(multi, *J* (Hz))**
8	6.62 (s)	6.59 (s)
2'/6'	8.15 (dd, 9.0, 2.4)	8.12 (d, 9.0)
3'/5'	7.03 (dd, 7.0, 2.4)	7.00 (d, 9.0)
1"	3.40 (d, 7.2)	3.37 (d, 6.7)
2"	5.32 (m)	5.29 (tm, 6.7)
4"	1.83 (s)	1.97 (t, 7.3)
5"	1.98 (s)	2.06 (br q, 7.3)
6"	5.10 (m)	5.06 (br t, 7.3)
8"	1.77 (d)	1.85 (br t, 7.3)
9"	1.83 (s)	1.93 (br q, 7.3)

Table 3 (cont'd). NMR Spectroscopic Data of Compound **2**

Position	**Compound 2** δ_H **(multi, *J* (Hz))**	**Macagigantin*** δ_H **(multi, *J* (Hz))**
10"	5.04 (m)	5.00 (br t, 7.3)
12"	1.59 (s)	1.57 (br s)
13"	1.54 (s)	1.51 (br s)
14"	1.57 (s)	1.54 (br s)
15"	1.60 (s)	1.79 (br s)
5-OH	12.44 (s)	12.41 (s)
7-OH	9.71 (br s)	-
3-OH	7.98 (br s)	-
4'-OH	9.04 (br s)	-

Compound **2** NMR Spectra recorded at 600 MHz (^{1}H) in acetone-d_6

*Macagigantin NMR Spectra recorded at 500 MHz (^{1}H) in methanol-*d* [13]

Conclusion

The crude methanol extracts of *M. gigantea* showed a good acetylcholinesterase inhibitory activity. Phytochemical screening of the crude extracts showed a potential secondary metabolite which leads to the isolation and purification of schweinfurthin C **(1)** and macagigantin **(2).** This suggests that this plant could be used as a potential treatment for Alzheimer's disease. However, further studies on the pharmacology of the isolated compounds are needed to find which bioactive compound is responsible for the acetylcholinesterase inhibitory activity of this species.

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References

1. Yang, D. S., Peng, W. B., Yang, Y. P., Liu, K. C., Li, X. L. and Xiao, W. L. (2015). Cytotoxic prenylated flavonoids from *Macaranga indica*. *Fitoterapia*, 103: 187-191.
2. Johari, M. S. M., Ahmat, N., Kamarozaman, A. S. and Isa, M. H. M. (2019). Prenylated flavonols from the leaves of *Macaranga gigantea* (Rchb. F. & Zoll.). *Scientific Research Journal*, 16(1): 29-40.
3. Kamarozaman, A. S., Ahmat, N., Rahman, N. F. A. and Yen, K. H. (2018). Prenylated dihydrostilbenes from *Macaranga heynei* (Euphorbiaceae). *Malaysian Journal of Analytical Sciences*, 22(2): 258-263.
4. Lim, T. Y., Lim, Y. Y. and Yule, C. M. (2014). Bioactivity of leaves of *Macaranga* species in tropical peat swamp and non-peat swamp environments. *Journal of Tropical Forest Science*, 2014: 134-141.
5. Aminah, N. S., Kristanti, A. N. and Tanjung, M. (2014). Antioxidant activity of flavonoid compounds from the leaves of *Macaranga gigantea*. *Journal of Chemical and Pharmaceutical Research*, 6(6): 688-692.

6. Heckroth, H. P., Fiala, B. and Maschwitz, U. (2016). Integration of scale insects (Hemiptera: Coccidae) in the south-east Asian ant-plant (*Crematogaster* (Formicidae)-*Macaranga* (Euphorbiaceae)) System. *Entomologica*, 33: 287-295.
7. Norfaizal, G. M., Khalijah, H. and Ruzi, A. M. (2012). Leaf anatomical study of five *Macaranga* species (Euphorbiaceae). *Journal of Tropical Agriculture & Food Science*, 40(2): 289-296.
8. Magadula, J. J. (2014). Phytochemistry and pharmacology of the genus *Macaranga*: A review. *Journal of Medicinal Plants Research*, 8(12): 489-503.
9. Pandey, A. and Tripathi, S. (2014). Concept of standardization, extraction and pre phytochemical screening strategies for herbal drug. *Journal of Pharmacognosy and Phytochemistry*, 2(5): 115-119.
10. Ellman, G. L., Courtney, K. D., Andres Jr, V. and Featherstone, R. M. (1961). A new and rapid colourimetric determination of acetylcholinesterase activity. *Biochemical pharmacology*, 7(2): 88-95.
11. Salles, M. T., Viana, F. V., Van De Meent, M., Rhee, I. K. and Verpoorte, R. (2003). Screening for acetylcholinesterase inhibitors from plants to treat Alzheimer disease. *Química Nova*, 26: 1-7.
12. Beutler, J. A., Shoemaker, R. H., Johnson, T. and Boyd, M. R. (1998). Cytotoxic geranyl stilbenes from *Macaranga schweinfurthii*. *Journal of Natural Product,* 61: 1509-1512.
13. Tanjung, M., Hakim, E. H., Mujahidin, D., Hanafi, M. and Syah, Y. M. (2009). Macagigantin, a farnesylated flavonol from *Macaranga gigantea*. *Journal of Asian natural products research*, 11(11): 929-932.
14. Howes, M. J. R. and Perry, E. (2011). The role of phytochemicals in the treatment and prevention of dementia. *Drugs & Aging*, 28(6): 439-468.
15. Kamarozaman, A. S., Ahmat, N., Isa, S. N. M., Hafiz, Z. Z., Adenan, M. I., Yusof, M. I. M. and Latip, J. (2019). New dihydrostilbenes from *Macaranga heynei* IM Johnson, biological activities and structure-activity relationship. *Phytochemistry Letters*, 30: 174-180.