Caffeoylquinic acids in leaves of selected Apocynaceae species: Their isolation and content

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ABSTRACT

Background: Three compounds isolated from the methanol (MeOH) leaf extract of Vallaris glabra (Apocynaceae) were those of caffeoylquinic acids (CQAs). This prompted a quantitative analysis of their contents in leaves of V. glabra in comparison with those of five other Apocynaceae species (Alstonia angustiloba, Dyera costulata, Kopsia fruticosa, Nerium oleander, and Plumeria obtusa), including flowers of Lonicera japonica (Japanese honeysuckle), the commercial source of chlorogenic acid (CGA). Materials and Methods: Compound were isolated by column chromatography, and identified by NMR and MS analyses. CQA content of leaf extracts was determined using reversed-phase HPLC. Results: From the MeOH leaf extract of V. glabra, 3-CQA, 4-CQA, and 5-CQA or CGA were isolated. Content of 5-CQA of V. glabra was two times higher than flowers of L. japonica, while 3-CQA and 4-CQA content was 16 times higher. Conclusion: With much higher CQA content than the commercial source, leaves of V. glabra can serve as a promising alternative source.

Key words: Apocynaceae, caffeoylquinic acids, chlorogenic acid, Vallaris glabra

INTRODUCTION

The family of Apocynaceae consists of about 250 genera and 2000 species of tropical trees, shrubs, and vines.[1,2] Almost all species of the family produce milky sap. Other characteristic features are simple, opposite or whorled leaves; large, colorful, and slightly fragrant flowers with five contorted lobes; and fruits are in pairs. The family has now been enlarged from two to five subfamilies with the inclusion of species of Asclepiadaceae.[3]

In traditional medicine, Apocynaceae species are used to treat gastrointestinal ailments, fever, malaria, pain, and diabetes.[1] Apocynaceae species have also been reported to demonstrate anticancer and antiplasmodial properties.

Our earlier study on the antiproliferative (APF) activity of sequential leaf extracts of ten Apocynaceae species showed that Alstonia angustiloba, Calotropis gigantea, Catharanthus roseus, Nerium oleander, Plumeria obtusa, and Vallaris glabra displayed positive inhibition.[4,5] Allamanda cathartica, Cerbera odollam, Dyera costulata, and Kopsia fruticosa did not display any APF activity. Leaves were sequentially extracted with hexane (Hex), dichloromethane (DCM), and methanol (MeOH). DCM and DCM: MeOH (1:1) leaf extracts of V. glabra inhibited all six cancer cell lines of MCF-7, MDA-MB-231, HeLa, HT-29, SKOV-3, and HepG2, while the MeOH extract inhibited MCF-7 and HepG2 cells. Against MCF-7 cells, growth inhibition of DCM and DCM: MeOH extracts of V. glabra was stronger than standard drugs of xanthorrhizol and comparable to tamoxifen. Results showed that leaves of V. glabra possessed strong and broad-spectrum APF properties.

Sequential leaf extracts of all five Apocynaceae species (A. angustiloba, C. gigantea, D. costulata, K. fruticosa, and V. glabra) were effective against K1 strain of Plasmodium falciparum.[6] Three species (C. gigantea, D. costulata, and K. fruticosa) were effective against 3D7 strain. Against K1 strain, all four extracts of V. glabra displayed effective APM activity.

In this study, three compounds isolated from the MeOH leaf extract of V. glabra were those of caffeoylquinic acids. This
prompted a quantitative analysis of their contents in leaves of *V. glabra* in comparison with those of five other Apocynaceae species and flowers of *Lonicera japonica* (Japanese honeysuckle), the commercial source of chlorogenic acid.

**MATERIALS AND METHODS**

**Plant materials**
The six Apocynaceae species studied were *A. angustiloba*, *D. costulata*, *K. fruticosa*, *N. oleander*, *P. obtusa*, and *V. glabra* [Figure 1]. Their common or vernacular names and brief descriptions are given in Table 1. Leaves of the species studied were collected in June 2012 from Sunway, Puchong, or Kepong, all in the state of Selangor, Malaysia. Identification of species was verified by Dr. H.T. Chan (Forest Research Institute Malaysia), and based on documented descriptions and illustrations. Voucher specimens of these species were deposited in the herbarium of Monash University Sunway Campus.

**Extraction of leaves**
For isolation of compounds from MeOH extracts, leaves (40 g) of *V. glabra* were freeze-dried overnight, ground, and extracted successively with Hex, DCM, DCM: MeOH (1:1), and MeOH. For each solvent (50 ml/g of sample), the suspension of ground samples was shaken for 1 h on the orbital shaker. After filtering, the samples were extracted two more times for each solvent. Solvents were removed with a rotary evaporator to obtain the dried extracts, which were stored at -20°C for further analysis.

For quantitative analysis of caffeoylquinic acid (CQA) content, fresh leaves (1 g) were powdered with liquid nitrogen in a mortar and extracted with 50 ml of 70% methanol. Extracts were filtered under suction, prepared in triplicate, and stored at 4°C for analysis, which were conducted within a week of extraction.

**Isolation of compounds**
MeOH leaf extract of *V. glabra* (40 g) was chromatographed on a MCI CHP-20P gel column with gradient H_2O-MeOH (0→100% MeOH) to obtain eight fractions (M1 to M8). Fraction M4 (0.69 g) was then subjected to Chromatorex C18 with gradient H_2O-MeOH (0→100% MeOH) to give two sub-fractions (M4-1 and M4-2). Sub-fraction M4-1 (0.60 g) was passed through Silica gel 60 with gradient CHCl_3:MeOH:H_2O (10:0:0→6:4:1) to give eight sub-fractions (M4-1-1 to M4-1-8). Sub-fraction M4-1-6 (0.51 g) was then subjected to MCI CHP-20P gel with gradient H_2O-MeOH (0→100% MeOH) to yield Compound 1 (38 mg), Compound 2 (9 mg), and Compound 3 (24 mg).

**Identification of compounds**
Compounds were dissolved in a deuterated solvent and subjected to ^1^H and ^13^C NMR analysis using a Bruker DRX 300 MHz spectrometer (300 MHz for ^1^H and 75 MHz for ^13^C). Chemical shifts were recorded in ppm (δ) using tetramethylsilane (TMS) as internal standard.

Compounds were subjected to electrospray ionization mass spectrometry (ESI-MS) using a Perkin Elmer Flexar SQ 300 mass spectrometer. Mass spectra were acquired in negative ion mode [M-H]. Analytes were introduced into the mass spectrometer by direct infusion. Mass up to 3000 m/z was measured.

**Analysis of CQA content**
Fresh leaf extract of *V. glabra* was analyzed for its CQA content using reversed-phase HPLC with comparison

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**Table 1: Common or vernacular names and brief description of Apocynaceae species**

| Species (common vernacular name) | Brief description |
|----------------------------------|------------------|
| *Alstonia angustiloba* Miq. (Pulai) | A medium-sized tree with leaves in whorls and having fine secondary veins |
| *Dyera costulata* Hook (Jelutong) | A tall timber tree with straight columnar bole, leaves in whorls and latex which was an important source of chewing gum |
| *Kopsia fruticosa* (Ker.) A. DC. (Pink kopsia) | A shrub with large glossy leaves and clusters of light pink flowers resembling those of *Ixora* |
| *Nerium oleander* L. (Oleander) | An ornamental shrub with thick narrow leaves in pairs or whors and bearing clusters of pink, red, or purple flowers |
| *Plumeria obtusa* L. (Frangipanni) | A tree producing dark green, glossy and oval leaves and white fragrant flowers with a yellow center |
| *Vallaris glabra* Kuntze (Bread flower) | A woody climber producing clusters of white flowers with a scent characteristic of leaves of pandan (*Pandanus amaryllifolius*) or fragrant rice |

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**Figure 1:** The six Apocynaceae species studied
made to leaf extracts of five other Apocynaceae species. 3-O-cafeoylquinic acid (3-CQA), 4-O-cafeoylquinic acid (4-CQA), and 5-O-cafeoylquinic acid (5-CQA) isolated from the MeOH leaf extract of V. glabra by column chromatography were used to identify and quantify the CQA content in the six species in the HPLC chromatogram. Leaves of L. japonica, known to have high CQA content, were used as positive control.

HPLC (Agilent Technologies 1200 Series) instrument with Agilent Zorbax SBC-18 column (4.6 × 250 mm) were used in the HPLC analysis. A 15-min linear gradient from 5→100% MeOH was used to elute samples at 1.2 ml/min. Mobile phases were acidified with 0.1% trifluoroacetic acid (TFA) for better resolution. A 20-μl loop was used for injection and elution was monitored at 280 nm. Commercially purchased HPLC standard of 5-CQA (chlorogenic acid) was used to construct the calibration curve. CQA content was determined from the calibration curve. CQA content was determined as mg CGAE/100 g.

As 3-CQA, 4-CQA, and 5-CQA all shared similar UV absorption pattern as the HPLC standard of 5-CQA, the amount of 3-CQA and 4-CQA present in the extracts can be inferred from the calibration curve of the HPLC standard of 5-CQA.

RESULTS AND DISCUSSION

Three compounds isolated from the MeOH leaf extract of V. glabra were 3-caffeoylquinic acid (3-CQA) or neochlorogenic acid, 4-caffeoylquinic acid (4-CQA) or cryptochlorogenic acid, and 5-caffeoylquinic acid (5-CQA) or chlorogenic acid (CGA). Their appearance, ESI-MS, and 1H and 13C NMR spectral data are as follows:

**Compound 1: 3-O-cafeoylquinic acid (3-CQA)**
Brownish amorphous powder; ESI-MS m/z 353.03 [M-H]–; 1H NMR (CD3OD, 300 MHz) quinic moiety δ: 4.70 (1H, m, H-4), 4.15 (1H, m, H-3), 4.09 (1H, m, H-5), 2.02 (1H, m, H-6), 1.91 (1H, m, H-2); caffeoyl moiety δ: 7.52 (1H, d, J = 15.9, H-8'), 6.92 (1H, m, H-2), 6.83 (1H, dd, J = 1.5, 8.1, H-6'), 6.65 (1H, d, J = 8.1, H-5'), 6.22 (1H, d, J = 15.9, H-7'); 13C NMR (CD3OD, 75 MHz) quinic moiety δ: 79.1 (C-4), 76.6 (C-1), 69.5 (C-3), 65.7 (C-5), 42.5 (C-6), 38.6 (C-2); caffeoyl moiety δ: 178.0 (COO-), 169.0 (C-9'), 149.6 (C-4'), 147.1 (C-3'), 146.8 (C-7'), 127.8 (C-1'), 122.9 (C-6'), 116.4 (C-5'), 115.3 (C-8'), 115.1 (C-2').

**Compound 2: 4-O-cafeoylquinic acid (4-CQA)**
Light brownish amorphous powder; ESI-MS m/z 353.03 [M-H]–; 1H NMR (CD3OD, 300 MHz) quinic moiety δ: 4.70 (1H, m, H-4), 4.15 (1H, m, H-3), 4.09 (1H, m, H-5), 2.02 (1H, m, H-6), 1.91 (1H, m, H-2); caffeoyl moiety δ: 7.52 (1H, d, J = 15.9, H-8'), 6.92 (1H, m, H-2), 6.83 (1H, dd, J = 1.5, 8.1, H-6'), 6.65 (1H, d, J = 8.1, H-5'), 6.22 (1H, d, J = 15.9, H-7'); 13C NMR (CD3OD, 75 MHz) quinic moiety δ: 79.1 (C-4), 76.6 (C-1), 69.5 (C-3), 65.7 (C-5), 42.5 (C-6), 38.6 (C-2); caffeoyl moiety δ: 178.0 (COO-), 169.0 (C-9'), 149.6 (C-4'), 147.1 (C-3'), 146.8 (C-7'), 127.8 (C-1'), 122.9 (C-6'), 116.4 (C-5'), 115.3 (C-8'), 115.1 (C-2').

**Compound 3: 5-O-cafeoylquinic acid (5-CQA)**
Cream colored amorphous powder; ESI-MS m/z 353.03 [M-H]–; 1H NMR (CD3OD, 300 MHz) quinic moiety δ: 5.19 (1H, m, H-5), 3.97 (1H, m, H-3), 3.51 (1H, m, H-4), 1.99 (1H, m, H-6), 1.75-1.83 (1H, m, H-2); caffeoyl moiety δ: 7.44 (1H, d, J = 15.6, H-8'), 6.88 (1H, d, J = 1.7, H-2'), 6.78 (1H, dd, J = 1.7, 7.8, H-6), 6.62 (1H, d, J = 8.1, H-5), 6.17 (1H, d, J = 15.9, H-7'); 13C NMR (CD3OD, 75 MHz) quinic moiety δ: 75.5 (C-1), 74.5 (C-5), 72.9 (C-4), 68.4 (C-3), 41.2 (C-6), 36.7 (C-2); caffeoyl moiety δ: 178.9 (COO-), 169.0 (C-9'), 149.4 (C-4'), 146.8 (C-3'), 146.7 (C-7'), 127.9 (C-1'), 123.0 (C-6'), 116.4 (C-5'), 115.7 (C-2'), 115.1 (C-8').

As 3-CQA, 4-CQA, and 5-CQA all shared similar UV absorption pattern as the HPLC standard of 5-CQA, the amount of 3-CQA and 4-CQA present in the extracts can be inferred from the calibration curve of the HPLC standard of 5-CQA.

The molecular structures of 3-CQA, 4-CQA, and 5-CQA are shown in Figure 2. They are esters of caffeic and quinic acids with 3-CQA having the caffeoyl group attached to carbon 3, and the OH groups at carbons 1, 3, and 5, while 5-CQA has the caffeoyl group at carbon 4, and the OH groups at carbons 1, 3, and 5, while 5-CQA has the caffeoyl group at carbon 5, and the OH groups at carbons 1, 3, and 4.

The isolation of CQAs from leaves of V. glabra represents the first report of CQAs in the genus Vallaris. Earlier studies have documented the occurrence of CQAs in Apocynaceae species. 5-CQA had been reported in leaves of Catharanthus roseus. In the same species, 3-CQA
and 5-CQA have been isolated from stems and leaves, and 4-CQA from petals.\textsuperscript{12} CGA was reported in leaves of \textit{Vinca major},\textsuperscript{13} and in stems and leaves of \textit{Trachelospermum jasminoides}.\textsuperscript{14} The content of 4-CQA and 5-CQA identified from leaves of \textit{Apocynum venetum} had been reported to be 0.0-0.7% and 2.1-3.9%, respectively.\textsuperscript{15}

The occurrence and contents of CQAs in fruits and vegetables have been compiled.\textsuperscript{16} Plants rich in CQAs include flowers of \textit{L. japonica} (Japanese honeysuckle), the commercial source of CGA,\textsuperscript{17} leaves of \textit{Ipomoea batatas} (sweet potato),\textsuperscript{18} and heads of \textit{Cynara scolymus} (artichoke).\textsuperscript{19}

In prunes, the contents of 3-CQA, 4-CQA, and 5-CQA were of the ratio 79:18:4.\textsuperscript{6} In plums, their contents were 541, 9, and 73 mg/kg, respectively.\textsuperscript{20} The contents of CQA in three Chinese traditional herbs were investigated.\textsuperscript{21} 5-CQA was dominant in leaves of \textit{Eucommia ulmoides} and flowers of \textit{L. japonica}. 3-CQA and 4-CQA dominated the CQAs in leaves of \textit{Houttuynia cordata}.

The antioxidant properties of CQAs are widely recognized, with those of CGA most studied. They have the ability to inhibit human low-density lipoprotein (LDL) oxidation,\textsuperscript{22,23} scavenge free radicals such as reactive oxygen and nitrogen species,\textsuperscript{24,25} to inhibit to lipid peroxidation,\textsuperscript{26} to chelate iron in iron-induced lipid peroxidation,\textsuperscript{27} and to protect against DNA breakage caused by monochloramine.\textsuperscript{28} In terms of \textit{in vitro} peroxidation of human LDL, both CGA and caffeic acid are equally effective antioxidants, with stronger activity than sinapic acid, ferulic acid, and \textit{p}-coumaric acid.\textsuperscript{29}

It was reported that the number of caffeoyl groups contributes to the scavenging activity of DPPH and superoxide radicals rather than the linkage positions of caffeoyl groups to the quinic moiety.\textsuperscript{31} This implies that diCQA would have stronger antioxidant activity than CQA.

Besides antioxidant properties, studies have shown that CQA display diverse bioactivities. CGA is known to have strong antimicrobial properties,\textsuperscript{32} and is an effective anti-inflammatory, analgesic, and antipyretic agent.\textsuperscript{33,34} Other bioactivities included anti-skin aging, anti-hypercholesterolemia, and anti-hyperglycaemia activities.\textsuperscript{35} CGA has been reported to be cytotoxic to oral tumor cell lines of human oral squamous cell carcinoma (HSC-2) and salivary gland tumor (HSG) cell lines.\textsuperscript{36} CGA isolated from stems of \textit{Euonymus alatus} has been reported to inhibit metallo-proteinase-9, suggesting its chemopreventive properties against cancer.\textsuperscript{37}

The CQA content of fresh leaf extracts of \textit{V. glabra} and five other Apocynaceae species was analyzed using reversed-phase HPLC and results are shown in Table 2. HPLC standard 5-CQA (chlorogenic acid) was used to construct the calibration curve. CQA content was determined using peak areas. The calibration equation of peak area (mAU*s) against concentration of CGA (mg/l) was \( y = 24.262x \) (R\(^2\) = 1.000). 5-CQA was eluted at 7.1 min on the HPLC. As 3-CQA and 4-CQA had similar retention times (RT) of 5.9 min when eluted, they were estimated as a single aggregate.

It is interesting to note that leaves of all the six Apocynaceae species contained significant amounts of chlorogenic acid. Highest content of 5-CQA was observed in \textit{N. oleander} (537 ± 103 mg CGA/100 g) followed by \textit{V. glabra} (353 ± 25 mg CGA/100 g), which were respectively three and two times higher than the amount of 5-CQA in flowers of \textit{L. japonica} (173 ± 13 mg CGA/100 g), the commercial source of CGA [Table 2, Figure 3]. The 5-CQA content of \textit{N. oleander} and \textit{V. glabra} leaves also surpasses \textit{Etlingera elatior} (294 ± 53 mg CGA/100 g) and \textit{I. batatas} reported to be 294 ± 53 and 115 ± 16 mg CGA/100 g,
respectively.\(^{[38]}\) Although, \(D.\) costulata had the highest CQA content, the 5-CQA content of \(D.\) costulata (253 ± 32 mg CGA/100 g) was comparable to that of \(V.\) glabra and \(K.\) fruticosa (270 ± 63 mg CGA/100 g). 5-CQA content of \(D.\) costulata, \(K.\) fruticosa, and \(P.\) obtusa (245 ± 60 mg CGA/100 g) were significantly higher than that of \(L.\) japonica. Leaves of \(A.\) angustiloba (155 ± 24 mg CGA/100 g) had comparable amounts of 5-CQA as \(L.\) japonica. 3-CQA and 4-CQA content of \(V.\) glabra (370 ± 15 mg CGA/100 g) was the highest among the species screened and about 16 times higher than that of the flowers of \(L.\) japonica (23 ± 2.2 mg CGA/100 g) [Table 2; Figure 3]. Leaves of \(N.\) oleander (47 ± 4.4 mg CGA/100 g), \(K.\) fruticosa (40 ± 9.9 mg CGA/100 g), and \(A.\) angustiloba (19 ± 2.8 mg CGA/100 g) had significantly higher 3-CQA and 4-CQA content than that of \(L.\) japonica. 3-CQA and 4-CQA content was not detected in leaves of \(D.\) costulata. The presence of other isomeric forms of CQA could account for the high amounts of CQA content in the methanol leaf extract of \(D.\) costulata.

**CONCLUSION**

3-CQA, 4-CQA, and 5-CQA or CGA were isolated from leaves of \(V.\) glabra. Compared to flowers of \(L.\) japonica (the commercial source of CGA), 5-CQA content was two times higher, and 3-CQA and 4-CQA content was about 16 times higher. With much higher CQA content than the commercial source, leaves of \(V.\) glabra can serve as a promising alternative source.

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**Table 2: Caffeoylquinic acid content of MeOH leaf extract of Vallaris glabra with comparison to five other Apocynaceae species (fresh weight)**

| Species           | 3-CQA and 4-CQA | 5-CQA |
|-------------------|-----------------|-------|
| Vallaris glabra   | 370 ± 15        | 353 ± 25 |
| Alstonia angustiloba | 19 ± 2.8       | 155 ± 24 |
| Dyera costulata   | ND              | 253 ± 32 |
| Kopsia fruticosa  | 40 ± 9.9        | 270 ± 63 |
| Nerium oleander   | 47 ± 4.4        | 537 ± 103 |
| Plumeria obtusa   | 14 ± 4.7        | 245 ± 60 |
| Lonicera japonica | 23 ± 2.2        | 173 ± 13 |

Caffeoylquinic acid (CQA) content in mg CGA/100 g of samples (fresh weight) was determined using reversed-phase HPLC. Values are means±SD (n=3). Flowers of Lonicera japonica were included as positive control. ND=not detected.
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