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Xanthones from *Garcinia mangostana* Linn. Pulp

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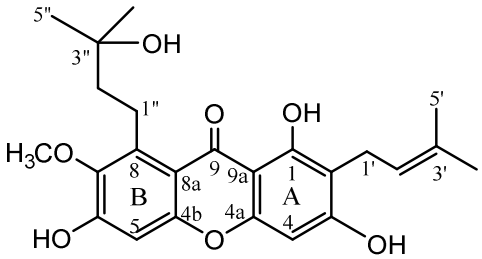
ABSTRACT

*In an earlier study, we isolated α-mangostin as the major xanthone and 3-isomangostin as a minor constituent of the pulp of the ripe fruit of Garcinia mangostana Linn. Further study on the pulp has led to the isolation of garcinone D (**1**). The structure of **1** was elucidated by extensive 1D and 2D NMR spectroscopy. Garcinone D was reported to exhibit anticancer property.*

Keywords: *Garcinia mangostana*, Guttiferae, garcinone D

INTRODUCTION

Garcinia mangostana Linn., the queen of fruits and commonly known as mangosteen, is a natural source of xanthones which are antioxidants, anti-inflammatory [1-2], antifungal [3], and are also used for chemoprevention [4-6]. Extracts and xanthones isolated from *G. mangostana* have antioxidant, antitumor, anti-allergic, anti-inflammatory, antibacterial, antifungal, and antiviral properties [7].



1

We earlier reported the isolation of α-mangostin, gartanin and 3-isomangostin from the pericarp of *G. mangostin* [8]. Recently, we reported the isolation of δ-tocotrienol, α-mangostin, 3-isomangostin, stigmasterol, triacylglycerols, β-sitosteryl-3β-glucopyranoside-6'-*O*-fatty acid esters, and stigmasteryl-3β-glucopyranoside-6'-*O*-fatty acid esters from the pulp; and stigmasterol, triacylglycerols, and linoleic acid from the seeds of *G. mangostana* [9]. This study reports on the isolation of garcinone D (**1**) from the dichloromethane extract of the pulp of the freeze-dried ripe fruit of *G. mangostana*.

MATERIALS AND METHODS

General Experimental Procedure

NMR spectra were recorded on a Varian VNMRS spectrometer in $CDCl_3$ at 600 MHz for ^{1}H NMR and 150 MHz for ^{13}C NMR spectra. Column chromatography was performed, with silica gel 60 (70-230 mesh). Thin layer chromatography, was performed with plastic backed plates coated with silica gel F_{254} and the plates were visualized by spraying with vanillin/H_2SO_4 solution followed by warming.

Sample Collection

Garcinia mangostana Linn. fruit was collected from Davao, Philippines in October 2015. The fruit was authenticated at the Botany Division, Philippine National Museum.

General Isolation Procedure

A glass column 18 inches in height and 1 inch internal diameter was used for the fractionation of the crude extracts. Eleven 20 mL fractions were collected. A glass column 12 inches in height and 0.5 inch internal diameter was used for the rechromatography of fractions from the crude extracts. 2 mL fractions were collected. Fractions with spots of the same R_f values were combined and rechromatographed in appropriate solvent systems until TLC pure isolates were obtained. Rechromatography and final purifications were conducted using Pasteur pipettes as columns. 1 mL fractions were collected.

Isolation of Garcinone D

The freeze-dried pulp (143.3 g) of *G. mangostana* was ground in a blender, soaked in CH_2Cl_2 for three days and then filtered. The filtrate was concentrated under vacuum to afford a crude extract (1.96 g) which was chromatographed by gradient elution with CH_2Cl_2, followed by increasing amounts of acetone at 10% increment by volume as eluents. The 60% acetone in CH_2Cl_2 fraction was rechromatographed (4 ×) using CH_3CN:Et_2O:CH_2Cl_2 (2:2:6, v/v) to afford **1** (3 mg) after trituration with petroleum ether.

Garcinone D (**1**): ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.27 (s, H-4), 6.81 (s, H-5), 3.41 (m, H_2-1'), 5.26 (m, H-2'), 1.82 (s, H_3-4'), 1.75 (s, H_3-5'), 3.41 (m, H_2-1"), 1.78 (m, H_2-2"), 1.31 (s, H_3-4"), 1.31 (s, H_3-5"), 13.62 (1-OH); ^{13}C NMR (150 MHz, $CDCl_3$): δ 160.55 (C-1), 108.69 (C-2), 161.82 (C-3), 93.33 (C-4), 155.06 (C-4a), 156.00 (C-4b), 101.64 (C-5), 154.69 (C-6), 142.54 (C-7), 138.48 (C-8), 112.00 (C-8a), 182.01 (C-9), 103.57 (C-9a), 21.17 (C-1'), 121.44 (C-2'), 135.66 (C-3'), 17.92 (C-4'), 25.84 (C-5'), 22.17 (C-1"), 44.40 (C-2"), 70.79 (C-3"), 29.25 (C-4"), 29.25 (C-5").

RESULTS AND DISCUSSION

Silica gel chromatography of the dichloromethane extract of the freeze-dried pulp of the ripe fruit of *G. mangostana* has led to the isolation of garcinone D (**1**). The structure of **1** was elucidated by extensive 1D and 2D NMR spectroscopy. Compound **1** indicated similar ^{1}H NMR resonances to α-mangostin [8]. The differences were the non-appearance of the benzylic methylene protons of the prenyl group attached to ring B at δ 4.07 (H_2-1") in α-mangostin and the appearance of more overlapping benzylic methylene protons at δ 3.41 in **1**. Furthermore, the vinylic proton at δ 5.26 (H-2") in α-mangostin was replaced by methylene protons at δ 1.78 in **1**. The allylic methyl groups at δ 1.67 (H_3-4") and 1.82 (H_3-5") in α-mangostin were replaced by two overlapping methyl singlets at δ 1.31 in **1**. These relatively deshielded methyl singlets suggested that they were bonded to a hydroxylated quaternary carbon. The change from a prenyl group with a double bond attached to ring B of α-mangostin to a hydroxylated prenyl group in **1** was supported by the ^{13}C NMR spectrum of **1**. The benzylic methylene carbon of the prenyl group attached to ring B of α-mangostin at δ 26.6 (C-1") was shielded to δ 21.4 in **1**. Moreover, the vinylic carbons at δ 123.5 (C-2") and 132.2 (C-3") in α-mangostin were shielded to δ 44.4 and 70.8, respectively in **1**. The ^{1}H and ^{13}C NMR assignments of **1** in $CDCl_3$ are given (see experimental). The protons bonded to carbons were deduced from HSQC. The structure of **1** was further supported by isolated spin systems from COSY and long-range correlations

deduced from HMBC. Previous literature reported the ^{1}H and ^{13}C NMR data of **1** in acetone-d_6 [10], DMSO-d_6 [11], and CD_3OD [12]. However, to the best of our knowledge this is the first report on the ^{1}H and ^{13}C NMR data of **1** in $CDCl_3$.

Garcinone D (**1**) exhibited cytotoxicity against the HT-29 cell line with an ED_{50} value of 2.3 µM and in an ELISA NF-κB assay, **1** inhibited p65 activation with an IC_{50} value of 3.20 µM [12]. It showed significant activity against CEM-SS cell line with an IC_{50} value of 3.2 µg/mL [13]. It was found to possess inhibitory activity using a cell free, enzyme-based microsomal aromatase inhibition assay. Furthermore, SKBR3 breast cancer cells which are known to express high levels of aromatase were found to be inhibited by **1** [14]. Garcinone D isolated from the young fruit (7 weeks maturity) of *G. mangostana* was also shown to exhibit cytotoxicity against epidermal carcinoma of the mouth (KB), breast cancer (BC-1), and small cell lung cancer (NCI-H187) with IC_{50} values of 3.56, 2.81 and 11.04 µg/mL, respectively [15]. Another study reported that **1** exhibited cytotoxicity to human nasopharyngeal carcinoma cell lines: CNE1 (IC_{50} = 16.28 µM), CNE2 (IC_{50} = 9.04 µM), SUNE1 (IC_{50} = 24.06 µM) and HONE1 (IC_{50} = 16.72 µM); human lung cancer cell lines: A549 (IC_{50} = 20.17 µM) and GLC82 (IC_{50} = 16.28 µM); human breast cancer cell line: MCF-7 (IC_{50} = 19.30 µM); and human hepatic cancer cell line: Bel 7402 (IC_{50} = 16.73 µM) [11], Furthermore, **1** showed bacteria neuraminidase inhibitory activity with an IC_{50} value of 2.2 µM [10].

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